EUROPEAN UROLOGY OPEN SCIENCE 59 (2024) 40–48

available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com

European Association of Urology

Andrology

Nomograms for Predicting Postoperative Sperm Improvements in Varicocele Patients

Abulaiti Maimaitiming [a,†], *Aidibai Muhemaiti* [b,†], *Yelisudan Mulati* [a], *Xiaodong Li* [a,*]

[a] Urology Department, The First Affiliated Hospital of Xinjiang Medical University, Xinjiang Clinical Research Center for Genitourinary System, Urumqi, China;
[b] Ultrasound Department, Medical Imaging Center, the First Affiliated Hospital of Xinjiang Medical University, Urumqi, China

Article info

Article history:
Accepted November 18, 2023

Associate Editor:
Silvia Proietti

Keywords:
Varicocele
Nomogram
Testicular elastic modulus
Testosterone
Sperm parameters

Abstract

Background: Varicocele is a condition that seriously affects male fertility. It can cause pathological changes in the testicles and affect their spermatogenesis and endocrine function.
Objective: To formulate nomograms to predict sperm improvements after microscopic varicocelectomy.
Design, setting, and participants: A retrospective analysis was conducted on varicocele patients who met the research criteria and were enrolled from March 2020 to June 2022. They were divided into a development and a validation cohort in a 2:1 ratio.
Outcome measurements and statistical analysis: Data on preoperative testicular atrophy index, bilateral testicular elastic modulus, testosterone, pre- and postoperative 6-mo total sperm count, sperm concentration, and sperm vitality were collected. An increase of $\geq$25% is considered a postoperative improvement in sperm parameters. Predictive nomograms were constructed through forward stepwise LR regression, based on independent risk factors filtered by univariate and multivariate logistic regression analyses. Receiver operating characteristic curve analysis, calibration curve, and decision curve analysis were employed to assess the performance of the models.
Results and limitations: The areas under the curve of nomograms for predicting the postoperative improvement of total sperm count, sperm concentration, and sperm vitality were 0.915, 0.986, and 0.924 respectively. The nomogram models demonstrated good predictive performance. The single-center sample size was a limitation of this study.
Conclusions: In this study, we developed effective predictive nomogram models for anticipating postoperative improvements in sperm quality among varicocele patients. These models offer a significant value in providing accurate predictions of surgical outcomes. However, it is crucial to conduct further external validation.

† These authors contributed to the work equally and should be regarded as co-first authors.
* Corresponding author. Urology Department, The First Affiliated Hospital of Xinjiang Medical University, Xinjiang Clinical Research Center for Genitourinary System, No. 137, Liyushan South Road, 830011 Urumqi, China. Tel.: +86 1896 3815 185.
E-mail address: lxd705@xjmu.edu.cn (X. Li).

https://doi.org/10.1016/j.euros.2023.11.008

Patient summary: In this study, a predictive nomogram model was constructed for assessing the improvement of sperm quality in varicocele patients after surgery. The model offered satisfactory results.

1. Introduction

Varicocele occurs when blood flows backward into the internal spermatic vein, resulting in the vascular dilation of the veins in the pampiniform plexus [1]. The congenital absence of spermatic vein valves or other compressive factors, including conditions such as "nutcracker syndrome," leads to the obstruction of venous blood flow. This obstruction results in swelling and pain in the testicles, affecting their physicochemical characteristics. Prolonged impairment of spermatogenesis and endocrine function can be expected as consequences. While the majority of patients with this condition do not experience any symptoms [2], individuals with severe symptoms may exhibit visibly dilated veins, resembling earthworms, on the surface of the scrotum. Varicocele is present in 15% of the normal population and 35–40% of infertile men [3]. Various theories have been proposed to explain the detrimental effects of varicocele on sperm quality. These theories suggest that heat exposure, decreased oxygenation, and toxin reflux contribute to the damage of the testicular ultrastructure, including interstitial cells and spermatogenic tubules. Ultimately, these factors negatively impact sperm quality [4,5], sperm function [6,7], testis histology [8–10], and reproductive hormones [5,11].

Consequently, varicocele has emerged as the most significant challenge to male fertility [12]. While the ability to conceive is still possible for many individuals with varicocele, it can adversely affect sperm quality in men. According to the European Association of Urology (EAU) guidelines on male infertility (2017 edition) [13], several recommendations are provided regarding the surgical treatment of varicocele. These recommendations include the following scenarios: (1) adolescent patients with progressive testicular atrophy detected during clinical examination and (2) clinical varicocele patients presenting with oligozoospermia, azoospermia, or infertility of unknown cause without any other identifiable factors. Moreover, it is noteworthy that the majority of patients diagnosed with varicocele in clinical settings present with a chief complaint of long-standing infertility. Consequently, sperm quality has become the paramount clinical parameter of concern in the treatment of male infertility attributed to varicocele, as it directly pertains to male reproductive health.

The present study endeavors to develop a nomogram model utilizing testicular ultrasonic parameters and testosterone levels to prognosticate the postoperative enhancement of sperm quality in varicocele patients.

2. Patients and methods

2.1. *Study design*

This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (K202304-03). A retrospective analysis was carried out on varicocele patients who met the research criteria from March 2020 to June 2022. All patients had undergone microscopical varicocelectomy operated by the same two experienced andrologists.

2.2. *Inclusion and exclusion criteria*

The inclusion criteria were as follows: (1) physical examination, two-dimensional gray ultrasound, and color Doppler ultrasound evidence of varicocele; (2) 18–40 yr old; (3) patients with varicocele who exhibit reduced fertility or are unable to conceive; and (4) varicocele patients who encounter substantial detriment to their overall quality of life, encompassing individuals enduring severe acute episodes characterized by pronounced swelling and intense pain, as well as those encountering recurring episode while concurrently demonstrating willingness to undergo surgical treatment.

The exclusion criteria were the following: patients with incomplete inspection, a previous surgical history, chronic diseases, other testicular or scrotal diseases, or a history of radiotherapy, chemotherapy, or hormone drug usage, and patients diagnosed with male infertility (infertility is defined as the failure to achieve a spontaneous pregnancy despite 1 yr of practicing regular sexual intercourse without a contraceptive) according to the World Health Organization (WHO) manual for the standardized investigation, diagnosis, and management of infertile male [14].

2.3. *Measurement of characteristics and follow-up*

The collected patient data were partitioned into development and validation cohorts at a 2:1 ratio. Characteristics such as age, body mass index (BMI), grade, pre- and postoperative 6-mo data of testicular atrophy index, bilateral testicular shear wave elastic modulus (Kpa), sperm parameters (total sperm count [10^6/ml], sperm concentration [10^6/ml], and sperm vitality [%]), and testosterone (ng/dl) were retrospectively collected.

Varicoceles were classified by the grading system of Dubin and Amelar [15] as grade I (palpable with Valsalva maneuver only), grade II (palpable at rest, without Valsalva), or grade III (visible while the patient is standing, without Valsalva). Testicular volume was calculated using the ellipsoid volume calculation formula ($\pi/6 \times$ length $\times$ width $\times$ height) [16]. The testicular atrophy index was calculated by the formula: *testicular atrophy index = (contralateral testis volume − affected testis volume)/contralateral testis volume* [17].

Indications for surgical treatment includes palpable varicocele, abnormal parameters of at least one sperm analysis, testicular pain, presence of testicular atrophy (>2 ml difference), failed multiple in vitro fertilization attempts, etc. [18].

The fifth edition of the WHO standard for sperm analysis [19] was used.

2.4. Statistical analysis

An increase of ≥25% is considered a postoperative improvement in sperm parameters. The included cohort was randomly divided into a development and a validation cohort at a ratio of 2:1.

The Kolmogorov-Smirnov test was used to establish the normality of continuous variables. The mean and standard deviation were used to describe regularly distributed continuous data. The median (interquartile range) was employed to represent continuous variables that were not normally distributed. The independent-sample *t* test is used to compare the means of two continuous normally distributed variables. The Student *t* test was used. The Mann-Whitney *U* test was applied to compare two continuous non-normally distributed variables. Number was given as the categorical variable (percentage). To compare categorical variables, the Fisher's exact test and the chi-square test were used.

Independent risk factors were screened by univariate and multivariate logistic regression analyses. The final model was determined by the forward LR stepdown process including all significant variables from the multivariate analysis. Nomograms were constructed using independent risk factors obtained from logistics regression analysis. Models' effectiveness was evaluated using a distinct validation cohort. Receiver operating characteristic curve analysis, plotted calibration curves, and decision curve analysis (DCA) were utilized to validate the discriminatory power, calibration and clinical utility, and advantages of these predictive models. The data were analyzed using IBM SPSS Statistics 23 (IBM Corp., Armonk, NY, USA) and R software (version 4.0.3; R Foundation for Statistical Analysis, Vienna, Austria). Statistical significance is defined as $p < 0.05$ in two-sided analyses.

3. Results

A retrospective analysis was carried out on 268 varicocele patients (180 in the development group and 88 in the validation group) who met the research criteria and were included from March 2020 to June 2022. All patients had undergone microscopical varicocelectomy that was performed by the same two experienced andrologists. Table 1 shows the baseline characteristics of the study population. There were no statistically significant differences between the two cohorts in baseline characters, as shown in Table 1.

The results of the univariate logistic analysis showed that age, preoperative grade, preoperative atrophy index, and left testicular elasticity modulus were positively correlated with the improvement in postoperative total sperm count, while preoperative testosterone levels, total sperm count, sperm concentration, and sperm vitality were negatively correlated with the improvement in postoperative total sperm count (Table 2). Preoperative grade, testicular atrophy index, and bilateral testicular elasticity modulus were positively correlated with the improvement in postoperative sperm concentration, while preoperative testosterone levels, total sperm count, sperm concentration, and sperm vitality were negatively correlated with the improvement in postoperative sperm concentration (Table 3). Preoperative grade, testicular atrophy index, and bilateral testicular elasticity modulus were positively correlated with the improvement in postoperative sperm vitality, while preoperative testosterone levels, total sperm count, sperm concentration, and sperm vitality were negatively correlated with the improvement in postoperative sperm vitality (Table 4).

The results of the multivariate logistic regression analysis indicated that age, testicular atrophy index, left testicular shear wave elastic modulus, testosterone, sperm concentration, and sperm vitality were independent risk factors for the improvement of postoperative total sperm count (Table 2). Right testicular shear wave elastic modulus, testosterone levels, total sperm count, and sperm concentration were independent risk factors for the improvement of postoperative sperm concentration (Table 3). Grade, left testicular shear wave elastic modulus, testosterone levels, sperm concentration, and sperm vitality were independent risk factors for the improvement of postoperative sperm vitality (Table 4).

The nomogram predictive models for postoperative total sperm count, sperm concentration, and sperm vitality, as well as their performance evaluation in the validation cohort, are presented in Figures 1–3, respectively. In the validation cohort, corresponding area under the curve values were 0.915, 0.986, and 0.924, respectively. The result shows that this model is highly accurate. Calibration plots of the corresponding nomograms in the development and validation cohorts for postoperative improvements in total sperm count, sperm concentration, and sperm vitality showed good calibrations. DCA proved these nomograms' clinical applicability, with good net benefits to varicocele patients. The efficacy evaluation in the development cohort can be found in Supplementary Figure 1.

4. Discussion

While numerous studies have demonstrated the impact of varicocele on sperm quality, the precise mechanisms underlying varicocele's effects on male reproductive function warrant further investigation. Theories positing abnormal scrotal temperature, metabolic waste reflux, and oxidative stress have been proposed to elucidate the pathophysiological mechanisms by which varicocele induces testicular changes. In addition to testicular and spermatic cord ultrasound evaluations, the improvement of sperm quality has gained increasing attention as a vital aspect in assessing male reproductive capacity during the postoperative follow-up of varicocele patients. Although fertility is influenced by both partners, varicocele remains the foremost risk factor for primary infertility in males.

According to current literature, it is clear that age and BMI [20–27], varicocele grade [28–31] and testicular elasticity modulus [32–35] have a definite impact on male fertility and sperm quality. Interestingly, the multivariate logistic regression analysis showed that BMI had no predictive value for the improvement of sperm parameters after surgery. Related reports have mentioned that obesity and its underlying mediators have a negative impact on sperm parameters, including sperm concentration, vitality, viability, and normal morphology [36]. However, Amann [37]

Table 1 – Baseline characteristics of the study population

Variable	Primary cohort (*n* = 180)		Validation cohort (*n* = 88)		*p* value
Age, yr (mean, SD)	29.94	7.549	29.03	7.363	0.354
BMI (mean, SD)	24.57	3.645	23.69	3.624	0.064
Grade (%)					0.32
I	46	25.56	30	34.09	
II	49	27.22	23	26.14	
III	85	47.22	35	39.77	
Preoprative					
TAI (mean, SD)	0.213	0.312	0.196	0.24	0.661
LTSWE (mean, SD)	5.72	0.965	5.6	0.952	0.323
RTSWE (mean, SD)	3.45	0.363	3.39	0.357	0.198
Testosterone (mean, SD)	13.408	4.331	13.475	4.41	0.909
After improvement (yes, no)					
TMC	145	35	75	13	0.349
SC	115	65	49	39	0.195
SV	137	43	71	17	0.399

BMI = body mass index; LTSWE = left testicular shear wave elastic modulus; RTSWE = right testicular shear wave elastic modulus; SC = semen concentration; SD = standard deviation; SV = semen vitality; TAI = testicular atrophy index; TMC = total semen count.

Table 2 – Logistic regression of prognostic factors for postoperative improvement in total sperm count

	Total sperm count					
	Univariate analysis					Multivariate analysis
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	0.878	0.836–0.922	<0.001	0.796	0.730–0.868	<0.001
BMI	0.952	0.875–1.035	0.251			
Grade			<0.001			
I	Ref	Ref	Ref			
II	5.818	2.451–13.813	<0.001			
III	10.182	4.354–23.813	<0.001			
Preoperative						
TAI	13.663	3.962–47.114	<0.001	7.21	1.840–28.255	0.005
LTSWE	2.801	1.871–4.193	<0.001	4.478	2.136–9.387	<0.001
RTSWE	0.829	0.343–2.003	0.677			
Testosterone	0.822	0.760–0.889	<0.001	0.834	0.735–0.947	0.005
TMC	0.946	0.925–0.968	<0.001			
SC	0.958	0.937–0.980	<0.001	1.062	1.013–1.115	0.014
SV	0.901	0.866–0.938	<0.001	0.926	0.862–0.995	0.036

BMI = body mass index; CI = confidence interval; LTSWE = left testicular shear wave elastic modulus; OR = odds ratio; Ref = reference; RTSWE = right testicular shear wave elastic modulus; SC = semen concentration; SV = semen vitality; TAI = testicular atrophy index; TMC = total semen count.

Table 3 – Logistic regression of prognostic factors for postoperative improvement in sperm concentration

	Sperm concentration					
	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.022	0.988–1.057	0.212			
BMI	0.983	0.919–1.051	0.618			
Grade			<0.001			
I	Ref	Ref	Ref			
II	1.083	0.544–2.157	0.820			
III	62.833	20.751–190.257	<0.001			
Preoperative						
TAI	5.866	2.158–15.940	0.001			
LTSWE	2.797	2.017–3.879	<0.001			
RTSWE	2.919	1.416–6.014	0.004	14.537	3.650–57.900	<0.001
Testosterone	0.723	0.662–0.790	<0.001	0.893	0.798–0.999	0.049
TMC	0.958	0.937–0.980	<0.001	0.829	0.783–0.878	<0.001
SC	0.851	0.818–0.886	<0.001	1.069	1.014–1.128	0.014
SV	0.899	0.869–0.930	<0.001			

BMI = body mass index; CI = confidence interval; LTSWE = left testicular shear wave elastic modulus; OR = odds ratio; Ref = reference; RTSWE = right testicular shear wave elastic modulus; SC = semen concentration; SV = semen vitality; TAI = testicular atrophy index; TMC = total semen count.

suggested that a high BMI (>25 kg/m^2) in men is associated with a poor total sperm count. Therefore, we consider that this might be related to the limited sample size involved in this study.

4.1. *Total sperm count*

Total sperm count reflects the ability of the testis to produce sperm. According to the literature, the total sperm count

Table 4 – Logistic regression of prognostic factors for postoperative improvement in sperm vitality

	Sperm vitality					
	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	0.965	0.930–1.001	0.059			
BMI	0.989	0.914–1.069	0.779			
Grade			<0.001			0.001
I	Ref	Ref	Ref	Ref	Ref	Ref
II	1.167	0.593–2.294	0.655	0.099	0.023–0.432	0.002
III	8.167	3.472–19.211	<0.001	0.394	0.015–10.051	0.573
Preoperative						
TAI	6.966	2.413–20.114	<0.001			
LTSWE	2.061	1.471–2.890	<0.001	1.809	1.018–3.214	0.043
RTSWE	0.559	0.240–1.302	0.177			
Testosterone	0.836	0.777–0.898	<0.001	0.851	0.745–0.972	0.017
TMC	0.949	0.929–0.969	<0.001			
SC	0.96	0.940–0.979	<0.001	1.137	1.046–1.235	0.002
SV	0.799	0.755–0.844	<0.001	0.673	0.594–0.763	<0.001

BMI = body mass index; CI = confidence interval; LTSWE = left testicular shear wave elastic modulus; OR = odds ratio; Ref = reference; RTSWE = right testicular shear wave elastic modulus; SC = semen concentration; SV = semen vitality; TAI = testicular atrophy index; TMC = total semen count.

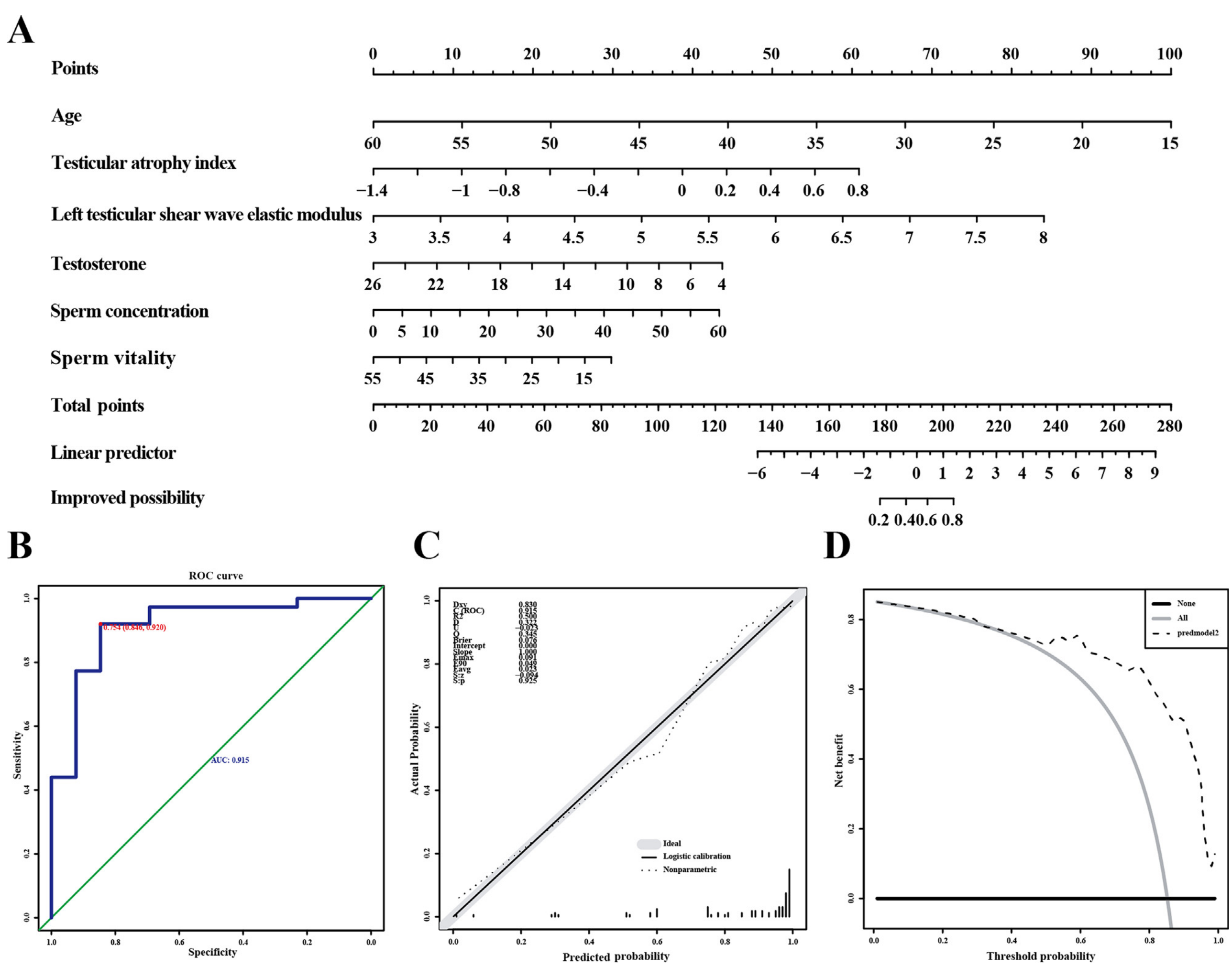

Fig. 1 – Nomogram predicting postoperative improvement in total sperm count and its performance evaluation in the validation group. (A) Postoperative total sperm count improvement predicted by the nomogram model. (B) Receiver operating characteristic curve analysis, (C) calibration plots, and (D) decision curve analysis were used to evaluate the performance of the postoperative total sperm count improvement predicted by the nomogram model in the validation group. AUC = area under the curve; ROC = receiver operating characteristics.

can accurately indicate the severity of male factor infertility. It is applicable not only for natural conception, but also for intrauterine insemination and in vitro fertilization [38,39]. Liu and colleagues' [40] research on total sperm count revealed a significant correlation between an increase in preoperative total sperm count and postoperative improve-

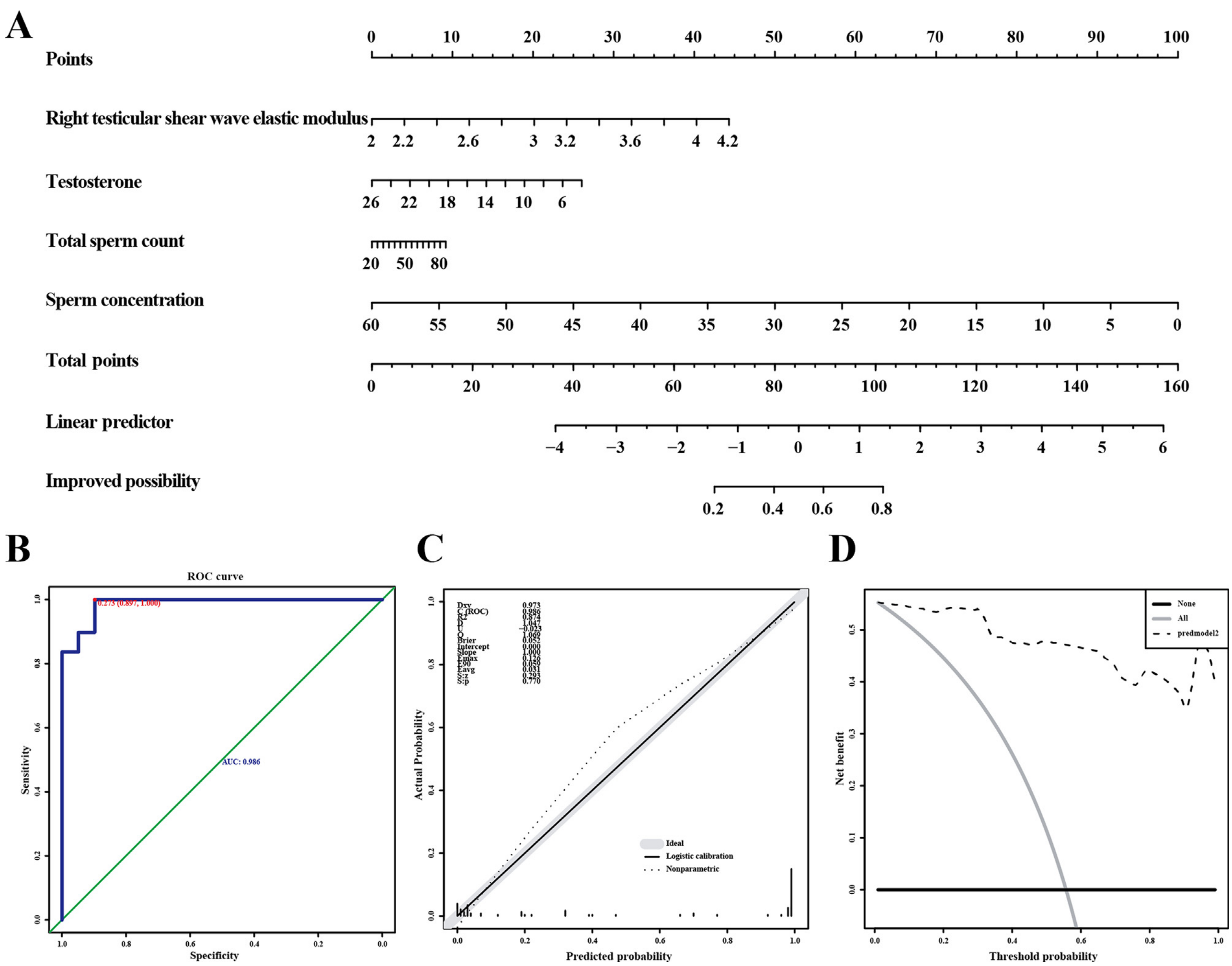

Fig. 2 – Nomogram predicting postoperative improvement in sperm concentration and its performance evaluation in the validation group. (A) Postoperative total sperm count improvement predicted by the nomogram model. (B) Receiver operating characteristic curve analysis, (C) calibration plots, and (D) decision curve analysis were used to evaluate the performance of the postoperative sperm concentration improvement predicted by the nomogram model in the validation group. AUC = area under the curve; ROC = receiver operating characteristics.

ments, suggesting that the total sperm count holds a predictive value for postoperative semen condition assessment. In addition, Wang et al. [41] showed that patients with a higher baseline sperm count after varicocele surgery had a more significant improvement in sperm parameters, and the improvement gap was positively correlated with the improvement in total sperm count after varicocele surgery. This result also suggests that the total sperm count reflects the overall sperm quality to some extent, and other changes such as sperm concentration and sperm vitality may be controlled by the degree of improvement in the total sperm count. Indicating when the total number of sperm reaches a certain size, the vitality of each individual sperm active might be better, so that the overall quality of sperm might be higher. This is also the basis for the assessment of total sperm count as a whole for sperm quality. This phenomenon could be contemplated in terms of sperm population size accompanied by an intensified competition. In such a scenario, when a certain number of spermatozoa coexist, each individual spermatozoon demonstrates enhanced vitality to successfully adapt to a demanding competitive environment, as there will always be a specific spermatozoon that emerges victorious in the final competition.

Our study results indicate that the preoperative testicular elastic modulus and testosterone levels have a predictive value for the postoperative total sperm count improvement [42]. Although the pathophysiology of varicocele and the molecular mechanisms involving testicular injury and sperm function impairment have not been elucidated fully, the prevailing consensus is that varicocele can inhibit testosterone biosynthesis and sperm chromosomal abnormalities, and elevate reactive oxygen species, leading to oxidative stress and endoplasmic reticulum stress, triggering germ cell apoptosis [43,44]. This indirectly corroborates the connection between testicular elastic modulus and testosterone as reflections of testicular tissue hardness and endocrine function with spermatogenic function. The testicular elastic modulus reflects the tissue hardness of the testicular parenchyma, and pathological mechanisms caused by varicocele-induced blood stasis and other disturbances in the physicochemical environment of the testis can

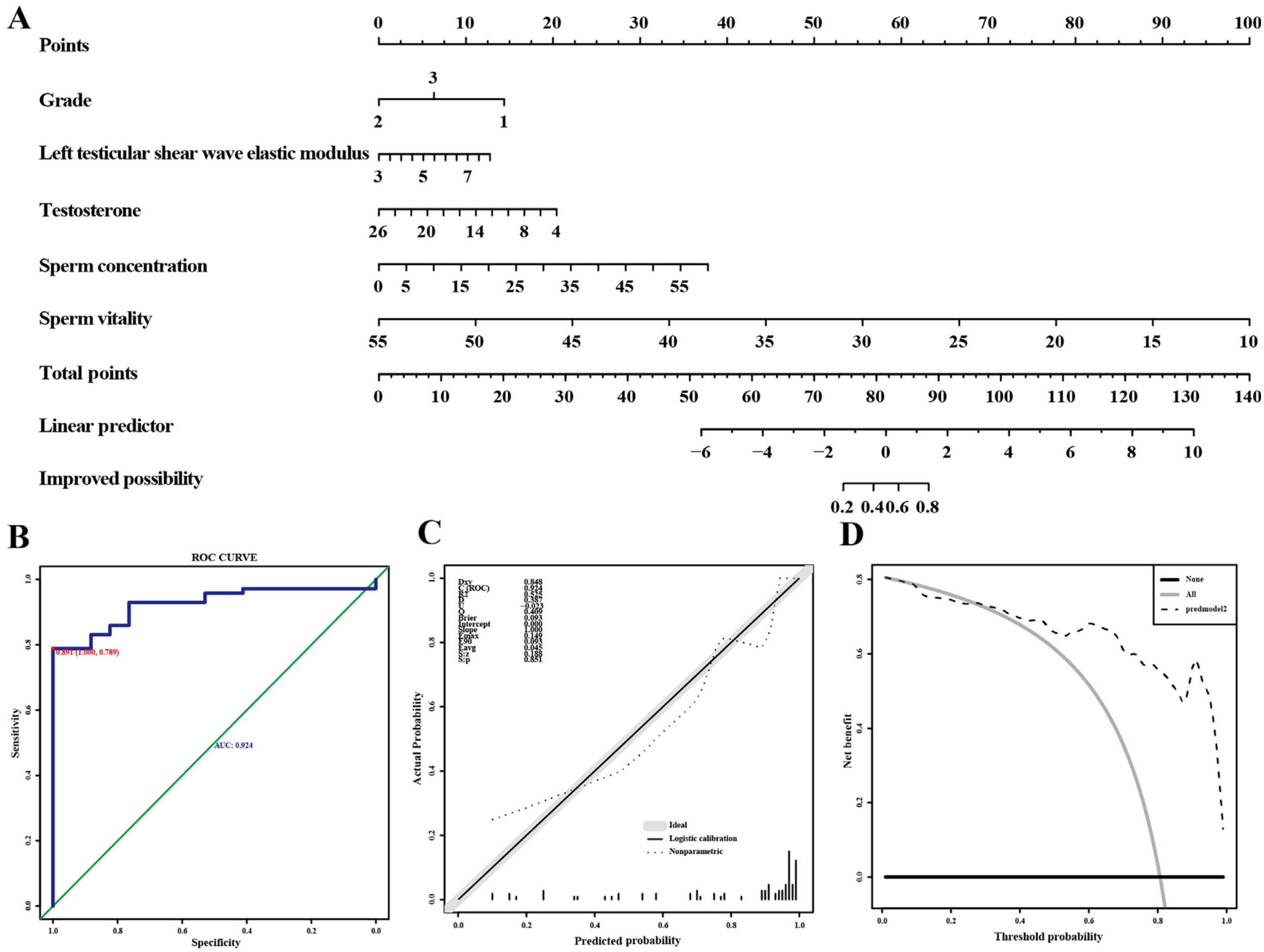

Fig. 3 – Nomogram predicting postoperative improvement in sperm vitality and its performance evaluation in the validation group. (A) Postoperative total sperm count improvement predicted by the nomogram model. (B) Receiver operating characteristic curve analysis, (C) calibration plots, and (D) decision curve analysis were used to evaluate the performance of the postoperative sperm vitality improvement predicted by the nomogram model in the validation group. AUC = area under the curve; ROC = receiver operating characteristics.

damage its ultrastructure [45]. Therefore, the predictive value of the testicular elastic modulus and testosterone levels for total sperm count is fundamentally grounded.

4.2. *Sperm concentration*

Sperm concentration is defined as the number of spermatozoa per unit volume of semen and is directly proportional to the number of sperm released and the volume of fluid diluting them [36]. According to the report of the sixth edition of the WHO laboratory manual on the examination and processing of human sperm, sperm concentration is correlated with male fertility but is not a direct indicator of testicular spermatogenic function. In contrast, the total sperm count is a better indicator of the spermatogenic ability of the testis [37]. This is because, during ejaculation, concentrated epididymal sperm are diluted by the fluid secreted by the accessory glands and are thus expelled from the body. Therefore, sperm concentration has higher variability. Meanwhile, reports have indicated that younger and older men might have the same sperm concentration, but different total sperm counts [46]. It has been reported that sperm concentration is related to the time to pregnancy [47] and pregnancy rates [48,49], and is a predictor of conception [50,51], but more data correlating sperm concentration with reproductive outcomes are needed. Slama et al. [47] used data from French sperm donors to develop a nonparametric model to describe the temporal decline in sperm concentration and then applied this model to 419 Danish couples planning their first pregnancy in 1992 to predict their time to pregnancy. Their results showed that both the sperm concentration and the probability of pregnancy decreased over the same period, but the decline in sperm concentration was significantly greater. Their attempt was very bold, but a larger sample size would be required to mitigate the changing effect of sperm concentration on the probability of pregnancy.

The results of this study indicate that the right testicular elastic modulus, testosterone, and total sperm count have a predictive value for the improvement of sperm concentration after surgery. In conclusion, this prediction model enriches the means of clinical evaluation for patients with varicocele.

4.3. *Sperm vitality*

Sperm vitality, among the essential factors for assessing sperm quality, often affected by flagellar defects [51], presence of epididymal pathological reactions, and infection [52], is also an important factor in the male reproductive health. Studies have shown that sperm vitality is closely related to sperm mitochondrial function [53], and mitochondrial sperm dysfunction is implicated in the pathogenesis of seminal oxidative stress [54]. According to the sixth edition of the WHO laboratory manual on the examination and processing of human sperm [55], test of sperm vitality, as estimated by assessing the membrane integrity of the cells, is mainly recommended when the total vitality is <40%. Sperm vitality test identifies whether the immotile spermatozoa are dead (necrozoospermia) or are alive but with abnormal vitality (asthenozoospermia) [56]. In the meta-analysis of sperm quality changes after varicocele surgery in adolescents, Ji [57] summarized six studies and also concluded that sperm concentration and sperm vitality were improved mildly to moderately after surgery.

Our research results indicate that preoperative staging, testicular atrophy index, left testicular elastic modulus, testosterone, preoperative sperm concentration, and preoperative sperm vitality have predictive values for the improvement of postoperative sperm vitality.

5. Conclusions

Testicular pathological changes caused by varicocele seriously threaten male fertility by affecting testicular spermatogenesis and endocrine function. Nomograms constructed in our study are different from many other studies for including predictors such as testicular atrophy index, testicular shear wave elastic modulus, and testosterone, which emphasized the predictive value of testicular physical characteristics and endocrine function on sperm parameters.

Despite the limitations of this study including a single-center retrospective design, insufficient sample size, and a limited number of predictive factors, this is an effective attempt to predict sperm quality in patients with varicocele based on testicular parameters and testosterone levels, which has a certain clinical value and is worthy of further exploration.

Author contributions: Xiaodong Li had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Maimaitiming.
Acquisition of data: Muhemaiti.
Analysis and interpretation of data: Li, Mulati.
Drafting of the manuscript: Maimaitiming.
Critical revision of the manuscript for important intellectual content: Li, Mulati.
Statistical analysis: Maimaitiming.
Obtaining funding: Li.
Administrative, technical, or material support: Mulati.
Supervision: Li.
Other: None.

Financial disclosures: Xiaodong Li certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This study was funded by the Natural Science Foundation of Xinjiang Uygur Autonomous Region (no. 2022D01C782; PI: Xiaodong Li).

Acknowledgments: We thank all the patients and participating authors for their contributions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.11.008.

References

[1] Jensen CFS et al.. Varicocele and male infertility. Nat Rev 2017;14:523–33.
[2] Paick S, Choi WS. Varicocele and testicular pain: a review. World J Mens Health 2019;37:4–11.
[3] Alsaikhan B et al.. Epidemiology of varicocele. Asian J Androl 2016;18:179–81.
[4] Gupta C et al.. Microscopic varicocelectomy as a treatment option for patients with severe oligospermia. Invest Clin Urol 2018;59:182–6.
[5] Damsgaard J et al.. Varicocele is associated with impaired semen quality and reproductive hormone levels: a study of 7035 healthy young men from six European countries. Eur Urol 2016;70:1019–29.
[6] Wang Y-J et al.. Relationship between varicocele and sperm DNA damage and the effect of varicocele repair: a meta-analysis. Reprod Biomed Online 2012;25:307–14.
[7] Vigil P et al.. Assessment of sperm function in fertile and infertile men. Andrologia 1994;26:55–60.
[8] Abdelrahim F et al.. Testicular morphology and function in varicocele patients: pre-operative and post-operative histopathology. Br J Urol 1993;72(5 Pt 1):643–7.
[9] Dubin L, Hotchkiss RS. Testis biopsy in subfertile men with varicocele. Fertil Steril 1969;20:51–7.
[10] Etriby A et al.. Testicular changes in subfertile males with varicocele. Fertil Steril 1967;18:666–71.
[11] Cayan S et al.. The effect of microsurgical varicocelectomy on serum follicle stimulating hormone, testosterone and free testosterone levels in infertile men with varicocele. BJU Int 1999;84:1046–9.
[12] Cozzolino DJ, Lipshultz LI. Varicocele as a progressive lesion: positive effect of varicocele repair. Hum Reprod Update 2001;7:55–8.
[13] Minhas S et al.. European Association of Urology guidelines on male sexual and reproductive health: 2021 update on male infertility. Eur Urol 2021;80:603–20.
[14] Rowe PJ, World Health Organization. WHO manual for the standardized investigation, diagnosis, and management of the infertile male. Cambridge, UK; New York, NY: Cambridge University Press (published on behalf of the World Health Organization); 2000. p. 91.
[15] Dubin L, Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril 1970;21:606–9.
[16] Kim SO et al.. Testicular catch up growth: the impact of orchiopexy age. Urology 2011;78:886–9.
[17] Niedzielski J, Pisarska K, Przewratil P. The usefulness of testicular atrophy index in the assessment of undescended testicle—preliminary report. Roczniki Akademii Medycznej W Bialymstoku 2003;48:112–4.

[18] Johnson D, Sandlow J. Treatment of varicoceles: techniques and outcomes. Fertil Steril 2017;108:378–84.
[19] Sánchez-Álvarez J, Cano-Corres R, Fuentes-Arderiu X. A complement for the WHO laboratory manual for the examination and processing of human semen (first edition, 2010). EJIFCC 2012;23:103–6.
[20] Sermondade N et al.. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. Hum Reprod Update 2013;19:221–31.
[21] Eisenberg ML et al.. The relationship between male BMI and waist circumference on semen quality: data from the LIFE study. Hum Reprod 2015;30:493–4.
[22] Hammiche F et al.. Body mass index and central adiposity are associated with sperm quality in men of subfertile couples. Hum Reprod 2012;27:2365–72.
[23] Belloc S et al.. High body mass index has a deleterious effect on semen parameters except morphology: results from a large cohort study. Fertil Steril 2014;102:1268–73.
[24] Xiao-Bin G et al.. The association between body mass index and varicocele: a meta-analysis. Int Braz J Urol 2021;47:8–19.
[25] Song Y et al.. Lower body mass index and higher height are correlated with increased varicocele risk. Andrologia 2019;51: e13391.
[26] Pasqualotto FF. Semen analysis: role of age and varicocele. J Postgrad Med 2007;53:1–2.
[27] Collodel G et al.. Influence of age on sperm characteristics evaluated by light and electron microscopies. Sci Rep 2021;11:4989.
[28] Abumelha S et al.. Can the body mass index predict varicocele recurrence post-intervention? Cureus 2021;13:e14892.
[29] Al-Ali BM et al.. Clinical parameters and semen analysis in 716 Austrian patients with varicocele. Urology 2010;75:1069–73.
[30] Ishikawa T, Fujisawa M. Effect of age and grade on surgery for patients with varicocele. Urology 2005;65:768–72.
[31] Scherr D, Goldstein M. Comparison of bilateral versus unilateral varicocelectomy in men with palpable bilateral varicoceles. J Urol 1999;162:85–8.
[32] Turna O, Aybar MD. Testicular stiffness in varicocele: evaluation with shear wave elastography. Ultrasonography 2020;39:350–5.
[33] Ryu YJ et al.. A preliminary study of shear-wave elastography for the evaluation of varicocele in adolescents and young adults. Ultrasonography 2022;41:131–9.
[34] Yüzkan S, Çilengir AH. Shear wave elastography for assessment of testicular stiffness in patients with varicocele: a prospective comparative study. J Med Ultrasound 2022;30:277–81.
[35] Abdelwahab K et al.. Role of preoperative testicular shear wave elastography in predicting improvement of semen parameters after varicocelectomy for male patients with primary infertility. Urology 2017;107:103–6.
[36] Baskaran S et al.. Diagnostic value of routine semen analysis in clinical andrology. Andrologia 2021;53:e13614.
[37] Amann RP. Evaluating spermatogenesis using semen: the biology of emission tells why reporting total sperm per sample is important, and why reporting only number of sperm per milliliter is irrational. J Androl 2009;30:623–5.
[38] Jang WS et al.. External validation of the post-varicocele repair semen analysis nomogram to predict total motile sperm count: a multicenter study. Andrologia 2020;52:e13809.
[39] Hamilton JAM et al.. Total motile sperm count: a better indicator for the severity of male factor infertility than the WHO sperm classification system. Hum Reprod 2015;30:1110–21.
[40] Liu X et al.. Nomogram for predicting semen parameters improvement after microscopic varicocelectomy in infertile men with abnormal semen parameters. J Pers Med 2022;13:11.
[41] Wang Q et al.. Outcome of varicocelectomy on different degrees of total motile sperm count: a systematic review and meta-analysis. Syst Biol Reprod Med 2019;65:430–6.
[42] Mulati Y et al.. Is there any predictive value of testicular shear wave elastic modulus in testicular functions for varicocele patients? Andrologia 2022;54:e14393.
[43] Karna KK et al.. The ameliorative effect of monotropein, astragalin, and spiraeoside on oxidative stress, endoplasmic reticulum stress, and mitochondrial signaling pathway in varicocelized rats. BMC Complement Altern Med 2019;19:333.
[44] Karna KK et al.. The role of endoplasmic reticulum stress response in male reproductive physiology and pathology: a review. World J Mens Health 2020;38:484–94.
[45] Santoro G et al.. Ultrastructural and immunohistochemical study of basal lamina of the testis in adolescent varicocele. Fertil Steril 2000;73:699–705.
[46] Ng KK et al.. Sperm output of older men. Hum Reprod 2004;19:1811–5.
[47] Slama R et al.. Time to pregnancy and semen parameters: a cross-sectional study among fertile couples from four European cities. Hum Reprod 2002;17:503–15.
[48] Zinaman MJ et al.. Semen quality and human fertility: a prospective study with healthy couples. J Androl 2000;21:145–53.
[49] World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. Fertil Steril 1996;65:821–9.
[50] Larsen L et al.. Computer–assisted semen analysis parameters as predictors for fertility of men from the general population. The Danish First Pregnancy Planner Study Team. Hum Reprod 2000;15:1562–7.
[51] Bonde JP et al.. Relation between semen quality and fertility: a population-based study of 430 first-pregnancy planners. Lancet 1998;352:1172–7.
[52] Chemes EH, Rawe YV. Sperm pathology: a step beyond descriptive morphology. Origin, characterization and fertility potential of abnormal sperm phenotypes in infertile men. Hum Reprod Update 2003;9:405–28.
[53] Travis AJ et al.. Targeting of a germ cell-specific type 1 hexokinase lacking a porin-binding domain to the mitochondria as well as to the head and fibrous sheath of murine spermatozoa. Mol Biol Cell 1998;9:263–76.
[54] La Vignera S et al.. FSH therapy for idiopathic male infertility: four schemes are better than one. Aging Male 2020;23:750–5.
[55] Who. WHO laboratory manual for the examination and processing of human semen. 6 ed. Geneva, Switzerland: WHO; 2021.
[56] Agarwal A et al.. Sperm vitality and necrozoospermia: diagnosis, management, and results of a global survey of clinical practice. World J Mens Health 2022;40:228–42.
[57] Ji ZY. Effect of varicocele on semen quality in young adults: a meta-analysis. Fujian Medical University; 2015.