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A Diagnostic Model to Improve the Predictability of Natural Pregnancy Potential in Patients with Oligoasthenospermia

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Data Collection B
Statistical Analysis C
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Manuscript Preparation E
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Background: Oligoasthenospermia is one of the major reasons for male infertility in clinical practice. Nevertheless, some patients with oligoasthenospermia show normal fertility. Currently, there is a lack of an effective method to distinguish patients with oligoasthenospermia showing normal fertility from those who lack natural fertility and should participate in *in vitro* fertilization and assisted reproduction.

Material/Methods: In this study, we collected semen and blood samples from 153 males of Shui nationality at reproductive age in Guizhou Province, southwest China. We measured the routine parameters for semen and some serological indicators. A clinical diagnosis model was then constructed to evaluate the fertility potential of oligoasthenospermia patients using a logistic stepwise regression method, which was then visualized with a nomogram.

Results: Our results showed that this model could effectively assess the natural pregnancy potential of patients with oligoasthenospermia, and its sensitivity and specificity were superior to those of a traditional model that used only sperm motility and count to assess male fertility potential (area under the curve=0.7626 *vs.* 0.6677). Additionally, we evaluated the clinical net benefit for patients with oligoasthenospermia at different risk scores in our model using decision curve analysis. The results showed that the net benefit was obtained at scores ranging from 0.1 to 0.6.

Conclusions: This comprehensive clinical prediction model can be used to determine whether infertile oligoasthenospermia patients lack natural fertility.

MeSH Keywords: Diagnosis • Oligospermia • Pregnancy

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Background

Idiopathic oligoasthenospermia is one of the main influencing factors of male infertility, but its mechanism is currently unclear [1]. At present, only sperm motility, count, and morphology are used clinically to diagnose male fertility [2]. Despite the difficulties, some oligoasthenospermia patients do have the opportunity to achieve natural pregnancy; thus, it is not necessary for these patients to participate in *in vitro* fertilization and assisted reproduction procedures. In contrast, for patients with oligoasthenospermia who cannot naturally achieve pregnancy, assisted reproduction should be implemented as early as possible [3]. However, currently, we only diagnose oligoasthenospermia, evaluate the severity of the disease, and determine whether *in vitro* fertilization should be performed according to sperm motility, count, and morphology [2], which cannot effectively distinguish between the above two types of patients. In this study, we collected additional serological indicators from routine clinical examinations, such as homocysteine (HCY), and constructed a comprehensive clinical predictive model that could be used to distinguish between fertile and infertile oligoasthenospermia patients. This model was clinically more effective in guiding the treatment of patients with oligoasthenospermia, improving their natural fertility, and providing advice on assisted reproduction in patients who lacked natural fertility.

Material and Methods

Patients and ethics

During the period from November 2011 to July 2012, we adopted an overall random sampling method to conduct a cross-sectional survey of all 18–55-year-old, married, and reproductive-age men in the Shui nationality area of Guizhou Province. After excluding individuals who did not desire to have children, had azoospermia, or had organic diseases such as cryptorchidism, varicocele, vas deferens disorders, and small testicles, 157 subjects were included in the analysis. Among them, men with normal sperm and normal fertility were included in the control group, men with oligoasthenospermia but having had offspring were included in the fertile oligoasthenospermia group, and men with oligoasthenospermia and no pregnancy success for more than 5 years were included in the infertile oligoasthenospermia group.

The study was approved by the Ethics Committee and Institutional Review Board of Shanghai Institute of Planned Parenthood Research. Consent was obtained from each participant after receiving a full explanation of the purpose and nature of all procedures used. The standards for collecting semen were as follows: subjects were asked to abstain from sex as much as possible for a maximum of 3–5 days; subjects were required to abstain from alcohol 4 days before collection; semen collection from infertile patients and the control group should be done at the same time and in the same season as often as possible; subjects should urinate and wash their hands and penis before semen collection. For blood collection, room temperature was maintained at 22–25°C, and the blood was collected from the same batch of research subjects at the same time. It was then stored in an anticoagulant tube, first in a 4°C refrigerator, then stored at –20°C for 8 h followed by –80°C for 2 weeks. The age range for blood collection was 20–50 years old, with an average age of 33 years.

Determination of serum reproductive hormone and HCY

Five milliliters of venous blood was collected, and then the serum was separated and stored at –20°C. Serum samples were measured by chemiluminescence. The indicators detected included follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), and HCY.

Determination of sperm quality

Semen samples were obtained by masturbation. Semen volume, pH value, density, sperm motility, and forward movement rate were determined using a WLJY-9000 automated color-sperm quality detection system according to the standards of the World Health Organization *Laboratory Manual for the Examination and Processing of Human Semen*, 5th edition, and the abnormal semen standard indicator was set according to the lower limit of the semen reference values provided.

Statistical analysis

Comparisons of parameters between patients and controls were assessed using the Wilcoxon test and Kruskal-Wallis test for continuous variables. The chi-square test was used for categorical variables.

A multivariable logistic regression model was generated with variable selection by backward elimination. For each patient, a total score was calculated, and then the outcome probability of each patient was calculated with a conversion function between the score and the outcome probability. The receiver operating characteristic (ROC) curve is recognized as a standard evaluation index. The area under the curve (AUC), with false positive rate as the abscissa and true positive rate as the ordinate, indicates the accuracy of the diagnostic test. The decision curve is a curve with threshold probability as the abscissa and net benefit as the ordinate. When the different evaluation methods reach a certain value, the positive probability of patient i is recorded as P_i; when P_i reaches a certain threshold (recorded as P_t), it is defined as positive, and some intervention should be taken [4,5].

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Table 1. Characteristics of normal fertility men and oligoasthenospermia.

Item		Normal	Infertility oligoasthenospermia			Fertility oligoasthenospermia				
		Statistics	Statistics	P Wilcox	P Kruskal	N (missing)	P Wilcox	P Kruskal	P* Wilcox	P* Kruskal
HCY	N (missing)	82 (0)	36 (0)	0.4386	0.4369	39 (0)	**0.0277**	**0.0275**	**0.0252**	**0.0249**
	Average (Q1–Q3)	13.445 (10.425–14.8)	12.872 (9.875–15.3)			16.621 (12.05–16.1)				
PR	N (missing)	82 (0)	36 (0)	**6.41E-18**	**6.25E-18**	39 (0)	**7.34E-19**	**7.16E-19**	**2.97E-05**	**2.90E-05**
	Average (Q1–Q3)	60.946 (53.925–67)	14.45 (11–19.025)			7.467 (0–13.65)				
PR+NP	N (missing)	82 (0)	36 (0)	**6.40E-18**	**6.24E-18**	39 (0)	**7.50E-19**	**7.31E-19**	**0.0011**	**0.0010**
	Average (Q1–Q3)	76.92 (71–83.75)	20.011 (14–25)			11.838 (2.25–19.4)				
density	N (missing)	82 (0)	35 (1)	**4.96E-09**	**4.87E-09**	39 (0)	**4.20E-08**	**4.13E-08**	0.9396	0.9353
	Average (Q1–Q3)	75.605 (51–86.8)	33.089 (13.1–44.55)			35.241 (9.15–45.5)				
age	N (missing)	79 (3)	36 (0)	**0.0005**	**0.0004**	38 (1)	**0.0064**	**0.0063**	0.5194	0.5159
	Average (Q1–Q3)	30.544 (25–35.5)	35.361 (30–39.25)			34.421 (29–39.5)				
FSH	N (missing)	77 (5)	36 (0)	**0.0325**	**0.0322**	36 (3)	**0.0142**	**0.0141**	0.8262	0.8218
	Average (Q1–Q3)	4.834 (3.25–6.12)	6.175 (3.9–8.004)			6.222 (4.228–7.09)				
LH	N (missing)	77 (5)	36 (0)	0.1842	0.1832	36 (3)	0.5562	0.5541	0.5136	0.5100
	Average (Q1–Q3)	5.065 (3.24–6.61)	6.019 (3.795–7.385)			5.451 (3.393–6.673)				
T	N (missing)	77 (5)	36 (0)	0.7886	0.7863	36 (3)	0.9166	0.9141	0.7270	0.7228
	Average (Q1–Q3)	5.853 (4.25–7.27)	5.861 (4.513–6.963)			5.665 (4.462–6.938)				
Normal sperm (percentage)	N (missing)	74 (8)	31 (5)	**4.01E-07**	**3.94E-07**	35 (4)	**4.52E-05**	**4.46E-05**	0.1140	0.1126
	Average (Q1–Q3)	0.287 (0.11–0.386)	0.103 (0.021–0.137)			0.13 (0.036–0.198)				
Teratozoo-sperm (percentage)	N (missing)	74 (8)	31 (5)	**4.01E-07**	**3.94E-07**	35 (4)	**4.52E-05**	**4.46E-05**	0.1140	0.1126
	Average (Q1–Q3)	0.713 (0.614–0.89)	0.897 (0.863–0.979)			0.87 (0.802–0.964)				
Round cell (percentage)	N (missing)	74 (8)	30 (6)	0.2415	0.2400	35 (4)	**0.0005**	**0.0005**	0.1122	0.1107
	Average (Q1–Q3)	0.025 (0.005–0.023)	0.047 (0.006–0.062)			0.06 (0.012–0.091)				

All statistical analyses were performed using the R programming language. $P<0.05$ was considered significant.

Patients and public involvement

Patients and the public were not involved in any aspect of this study.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. Samples from 157 subjects were analyzed, of whom 82 had normal fertility, 36 had fertile oligoasthenospermia, and 39 had infertile

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Table 2. Multivariable logistic regression model for successful natural conception.

	Estimate	Std. error	z Value	Pr (>|z|)
HCY	–0.125745411	0.085594226	–1.469087545	0.141809045
PR	0.203816615	0.056361961	3.616208687	0.000298949
FSH	–0.146793956	0.107902663	–1.360429416	0.173694075
Normozoospermia frequency	–3.553038021	2.673597978	–1.328935034	0.183869404

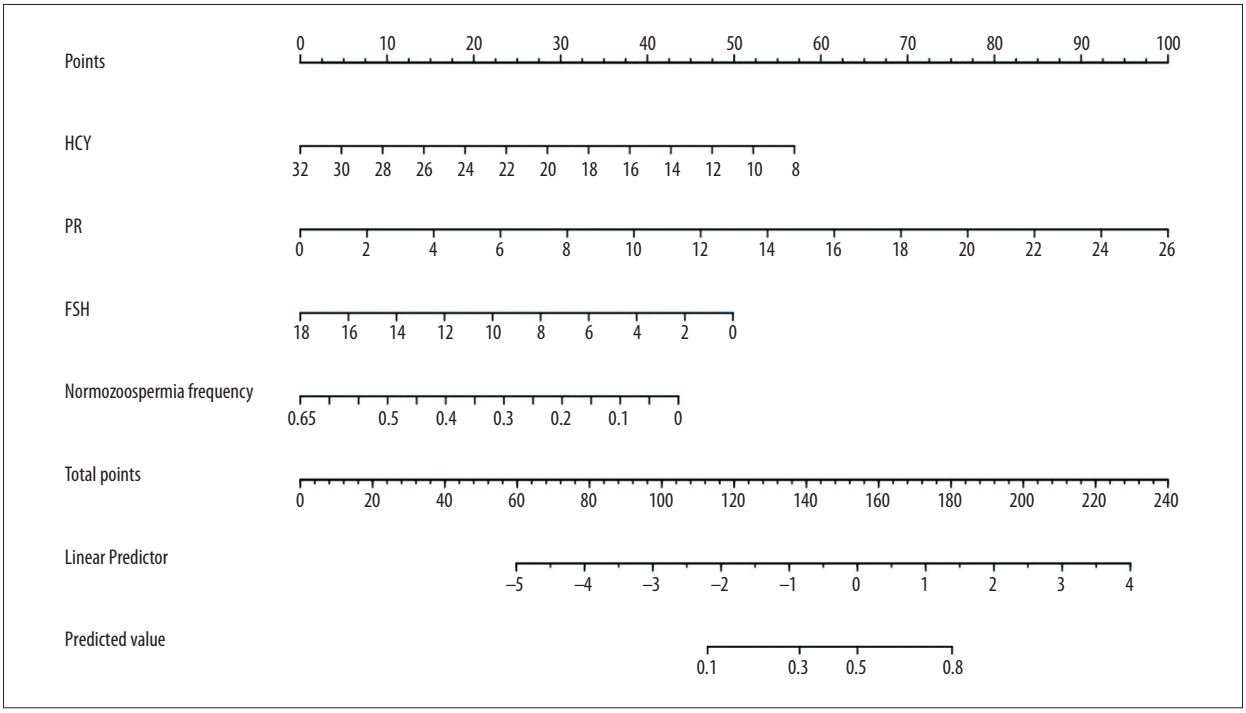

Figure 1. Nomogram for predicting natural pregnancy probabilities for oligoasthenospermia.

oligoasthenospermia. The variables studied included HCY, progressive motility (PR, %), PR + nonprogressive motility (%), density (10^6/mL), age, FSH, LH, T, percentage of normal sperm, percentage of malformed sperm, and percentage of round cells. Our results showed that there were no significant differences between the ages of patients with fertile and infertile oligoasthenospermia, and the levels of the three major hormones were FSH, 3.25–8.004; LH, 3.393–7.385; and T, 4.462–6.963.

Multivariable regression analysis and prognostic model construction

In this study, we established a predictive model to improve the accuracy for the current prognostic method using logistic regression. Then, we generated a predictive model to evaluate the fertility potential for patients with oligoasthenospermia by combining HCY, PR, and FSH with normozoospermia frequency, using a *P* value for the correlation coefficient <0.15 as the cutoff value (Table 2).

The point assignment of the nomogram for the probability of natural pregnancy for patients with oligoasthenospermia is shown in Figure 1. By adding up all points and locating them on the bottom scales, we can easily calculate the estimated probability of natural pregnancy for patients with oligoasthenospermia. When the corresponding variables for the diagnosed patients are substituted into the model, scores greater than 50% are recorded as infertile oligoasthenospermia, whereas those less than 50% are recorded as fertile oligoasthenospermia.

Efficacy of the diagnostic model

The nomogram showed valuable predictive power, with an AUC of 0.7626, sensitivity of 0.7188, and specificity of 0.8065 (Table 3). The area under the ROC curve was not affected by the prevalence and diagnostic critical value and thus can be used to comprehensively compare the accuracy of two diagnostic tests. In this study, we compared the accuracy of our multifactor model with that of one-factor predictive models.

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Table 3. Prediction properties of based on internal validation.

	Fertility oligoasthenospermia (predicted)	Infertility oligoasthenospermia (predicted)	Total
Fertility oligoasthenospermia (labeled)	23	9	32
Infertility oligoasthenospermia (labeled)	6	25	31
Total	**29**	**34**	**63**
	Ar=76.19%	Se=71.88%	Sp=80.65%

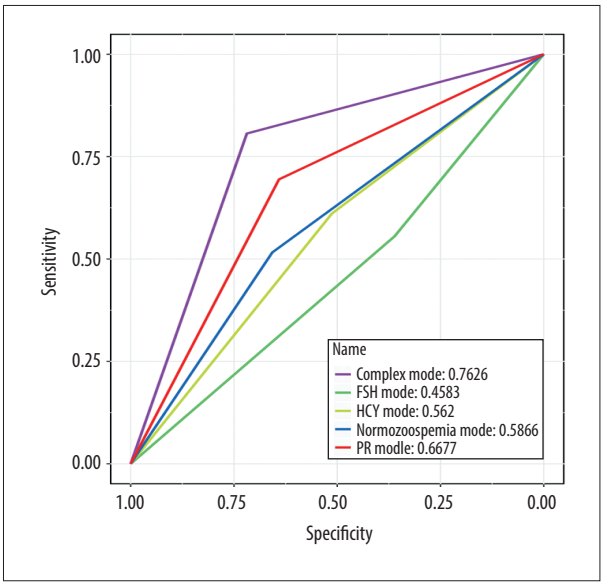

Figure 2. Receiver operating characteristic (ROC) curves for the created models.

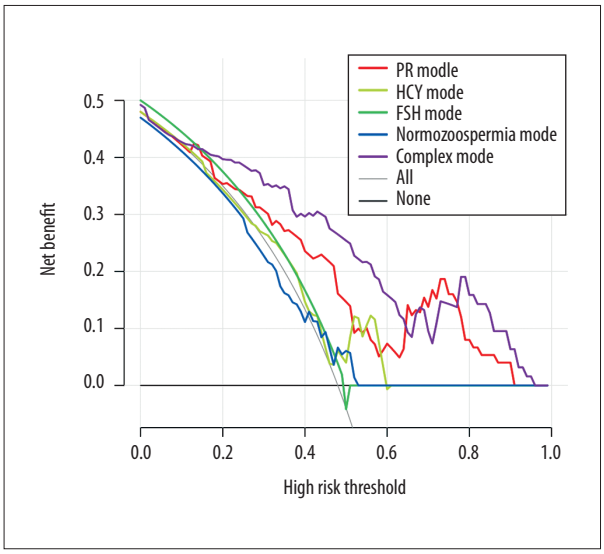

Figure 3. A hypothetical decision curve of net benefit of men with oligoasthenospermia.

The individual PR predictive indicator showed an AUC of 0.6677, whereas the individual sperm motility assessment model only showed an AUC of 0.5866 (Figure 2), which indicated that the comprehensive evaluation model was more accurate than the single-indicator evaluation models.

By inspecting the decision curve analysis plot shown in Figure 3, it is possible to find a clear net benefit gain over the entire range of thresholds when using the updated prognostic model compared with the baseline model or considering all patients (or no patients) at risk of infertile oligoasthenospermia.

Discussion

Oligoasthenospermia refers to the situation where the total number (or density) of spermatozoa and the percentage of forward-moving spermatozoa found during routine sperm testing are lower than the reference minimum values. Studies have shown that patients with this symptom generally show low fertility. A study by Li et al. collected 16 835 semen samples and revealed that oligoasthenospermia is related to infertility [6]. Liu et al. analysed the semen quality of 2810 infertile men in the Huzhou area of China and showed that oligoasthenospermia is one of the main factors of male infertility in this area [7].

At present, the treatment options for oligoasthenospermia mainly include drug treatment and assisted reproductive technology. The main purpose of drug treatment is to improve the quality of sperm and help patients conceive naturally. For instance, tamoxifen, coenzyme Q10, and traditional Chinese medicine qilin have all shown good clinical effects [8–10], improving the sperm quality of patients with oligoasthenospermia and helping them conceive naturally. However, it is difficult to determine which type of patient's sperm has the potential for improved quality by testing only sperm density and movement.

In this study, we found that, combined with sperm count, sperm motility, and other indicators, some routine items for clinical prognosis such as HCY and FSH could be used to construct a more accurate and effective predictive model that could effectively distinguish oligoasthenospermia patients who were

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able to conceive spontaneously from those who were unable to achieve natural pregnancy. Interestingly, when recruiting patients, we did not strictly limit the age of the respondents. Therefore, we considered age as one of the potential elements in fertility when modeling. A correlation was found between age and reproductive capacity of oligoasthenospermia patients; however, this correlation was lost in the process of constructing the model by regression analysis.

The model may help clinicians discriminate patients who should continue trying to conceive naturally from those who need assisted reproductive intervention. The strengths of our study include its randomized design and reasonable statistical methods. The study also has weaknesses that should be acknowledged. One of the weaknesses is the relatively small sample size, which may be due to our restrictive selection conditions. Another notable issue is that the study participants were limited to the Chinese Shui population, which restricted the generalizability of our findings. Therefore, further large-scale longitudinal cohort studies in multiracial and multiethnic populations are still needed. Furthermore, we attempted to control for confounding factors as much as possible but were unable to do so completely. For example, although we excluded the possible effects of alcohol and sample handling when recruiting patients, we did not consider environmental exposure factors such as potential infections, occupational factors, and heavy-metal pollution. These omissions could bias our results.

Conclusions

We used clinically routinely tested HCY, PR, FSH, and normal sperm count indicators to construct a comprehensive predictive model for infertile oligoasthenospermia. This model is superior to those built from single predictors, including sperm motility, the most commonly used clinical method of judging male fertility for distinguishing patients with fertility and infertility. However, because of the small sample size of this study, further large-scale multicenter studies are needed to obtain a more accurate evaluation model for clinical practice that would be of benefit for oligoasthenospermia patients.

Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interests

None.

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