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Developing a novel prediction model for the impact of varicocelectomy on postoperative fertility

Naser Yousefzadeh Kandevani (1,2), Farshad Namdari (1), Morteza Hamidi (1), Hossein Dialameh (3), Arya Behzadi (4)

(1) Department of Urology, Aja University of Medical Sciences, Tehran, Iran; (2) Yas Hospital complex (YHC), Tehran University of Medical Sciences (TUMS); (3) Tehran University of Medical Sciences (TUMS), Department of Urology, Tehran, Iran; (4) Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

The objective of this study was to evaluate inflammatory markers as predictors of fertility after varicocelectomy and to develop a prediction model. This prospective cohort was conducted on patients with varicoceles who were presented to the clinic of Imam Reza hospital of Tehran during 2019-2020. Semen analysis, complete blood count (CBC), and scrotal ultrasonography was requested. Patients with abnormalities of semen analysis were chosen as candidates for varicocelectomy. 6 months after the operation, semen analysis was repeated. Hematologic and semen analysis parameters were recorded at baseline and follow-up visits. Treatment success was defined as 50% increase in total motile sperm count (TMSC) in cases with preoperative TMSC> 5 million/cc or 100% increase in TMSC in cases with preoperative TMSC< 5 million/cc. Patients were then categorized into two groups based on treatment success and statistical analysis was performed on these two groups. 124 infertile patients with varicocele were evaluated in our study. 52 patients (41.93%) showed improvements in semen analysis after varicocelectomy. After univariate and multivariate analysis three parameters were used in our predictive model as body mass index (BMI)>23.70 kg/m2 (4 scores), neutrophil-lymphocyte ratio (NLR) >1.80 (3 scores), and TMSC<14.69 million (2 scores). A cut-off value of 5 was associated with an 87.5% sensitivity and an 84.6% specificity for the prediction of failure of varicocelectomy. Varicocelectomy can improve semen analysis parameters in almost all infertile men with varicocele. Using BMI, NLR, and baseline TMSC as the suggested scoring system can predict the success of varicocelectomy for improving fertility and determine the appropriate infertile candidates for surgery.

Key Words: Varicocelectomy; neutrophil-to-lymphocyte ratio; semen analysis; motile sperm.

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Infertility is one of the major problems being dealt with in health systems around the world. Estimations reveal a rate of 15% infertility for couples of reproductive ages. 40-50% of these infertile cases can be attributed to the male factor infertility.[1] While the majority of male infertility cases are idiopathic, varicocele ranks the first among identifiable causes in these patients.[2,3] Varicocele is a condition characterized by abnormal dilatation and tortuosity of the pampiniform venous plexus and the internal spermatic vein.[4] Varicocele is reported to be found in around 15% of the general population. Its prevalence rate is approximately 35% and 75% in primary and secondary infertile men, respectively.[4] Several theories have been proposed to explain the impact of varicocele on infertility which include thermal dysregulation of the testis, hypoxia due to blood stagnation in spermatic veins, presence of adrenal metabolites, dilution of substrates in testis, and higher levels of reactive oxygen species derived from sperm.[5-7] The influence of varicocele repair on fertility is a matter of debate. Many studies have stated that surgical treatment of varicocele yields favorable alterations in semen parameters, but there is not consensus in literature, some reports having not supported the beneficial impact of varicocele repair on male fertility.[8-10] Guidelines recommend that infertile men with clinically evident varicocele and at least one abnormality in semen parameters should undergo surgical repair of varicocele.[11] Some studies have shown that varicocele

Table 1. *Baseline demographic and hematologic variables*

Parameter	Group 1	Group 2	p-value
Marital status			
- Single	40 (76.9%)	60 (83.3%)	0.373
- Married	12 (23.1%)	12 (16.7%)	
Age	21.92±2.67	22.66±3.16	0.171
BMI	23.06±2.13	26.04±3.54	0.000
Hypotrophy of testis	4 (7.7%)	4 (5.6%)	0.373
Grade			
- 3	48 (92.3%)	68 (94.4%)	0.633
- 2	4 (7.7%)	4 (5.6%)	
Side			
- Left	44 (84.6%)	72 (100%)	0.001
- Right	8 (15.4%)	0 (0%)	
TTV	30.87±4.78	30.33±5.21	0.559
WBC	6.91±1.68	6.67±1.00	0.328
PLT	214.61±43.23	204.11±37.94	0.154
Neutrophil	57.23±7.49	55.77±5.85	0.228
Lymphocyte	36.84±7.53	37.55±5.73	0.553
PDW	13.06±0.73	13.16±0.84	0.495
MPV	9.44±1.33	9.56±1.07	0.598
NLR	1.68±0.68	2.28±0.43	0.000
PLR	6.16±2.10	5.64±1.89	0.157

grade in addition to the presence of reflux and retrograde flow can predict abnormalities in semen parameters and help identify patients who will benefit from surgery.[12] Total testicular volume (TTV) and testicular volume differential (TVD) have also been suggestive of future infertility in studies.[13] Some authors regard varicocele as a vascular and inflammatory disease. In line with this theory, they have evaluated inflammatory hematologic parameters such as the number and size of platelets and white blood cells and their association with varicocele and response to surgery. Increases in mean platelet volume have been introduced as a risk factor in vascular pathologies such as myocardial infarction, coronary atherosclerosis, and diabetes mellitus type II.[14] The coexistence of vascular disorders and varicocele has been reported in several studies. Thus, the quest for finding an association between mean platelet volume (MPV) status and varicocele led to several studies which reported the relationship of MPV with the development or grade of varicocele.[15-16] The neutrophil-to-lymphocyte ratio (NLR) is also another marker that is indicative of various inflammatory or vascular pathologies. NLR has also been studied in varicocele and was shown that NLR can independently predict varicocelectomy outcomes and the influence of the surgical intervention on semen parameters.[17] While there are numerous predictive factors for the impact of varicocelectomy on fertility, a prediction model combining all these factors into a score is highly appreciated for clinical application and treatment planning. In this study, we aimed to evaluate inflammatory markers as predictors of fertility after varicocelectomy and to develop a prediction model for this purpose.

Materials and Methods

Study Design and patients' populations

This prospective cohort was conducted on patients with varicocele of grade II or higher, who were presented to the urology clinic of Imam Reza hospital of Tehran during 2019-2020. This study had been reviewed and approved by "Ethics committee for research of AJA University of Medical Sciences" and the ethical code of study is IR.AJAUMS.REC.1399.128. After approval of the ethics committee, eligible patients signed informed consent and then were enrolled in the study. Due to the COVID-19 pandemic state at the time of study and changes in protocols of patients' admission at hospitals, all patients were screened for COVID-19 before hospitalization. In patients who were diagnosed with COVID-19 infection, the surgery was postponed for at least 2 weeks. Semen analysis with 2-3 days of abstinence, complete blood count (CBC), and scrotal ultrasonography was requested for all patients. Varicocele grade and size of testes were measured with physical examination and ultrasonographic findings. Platelets' count, mean platelet volume (MPV), platelet distribution width (PDW), neutrophil-to-lymphocyte ratio (NLR), and white blood cells (WBC) count were documented. In semen analysis, total semen volume, total sperms' count, total motile sperms' count (TMSC), and percentage of sperms with normal morphology were

Table 2. *Semen analysis parameters at baseline and after varicocelectomy*

Parameter		Group 1	Group 2	p-value
Sperm count	Baseline	38.05±24.27	34.11±26.39	0.271
	Postoperative	58.11±33.89	56.07±36.28	0.609
	p-value	0.001	0.001	
Sperm progressive motility	Baseline	33.79±18.41	37.98±20.18	0.613
	Postoperative	59.88±16.67	39.32±16.95	0.041
	p-value	0.012	0.783	
Sperm normal morphology	Baseline	11.08±11.07	9.35±10.27	0.229
	Postoperative	17.38±22.34	14.42±23.14	0.131
	p-value	0.022	0.030	
Total motile sperm count (TMSC)	Baseline	16.45±9.96	11.43±12.13	0.030
	Postoperative	33.89±20.62	16.82±20.75	0.044
	p-value	0.001	0.039	

recorded. Patients with abnormalities of semen analysis were chosen as candidates for varicocelectomy. A single senior surgeon with inguinal approach and use of loop magnifier performed all surgeries. We evaluated the association of elevation of inflammatory markers with varicocele severity and size of testis before operation. 6 months after the operation, semen analysis was repeated. Treatment success was defined as 50% increase in TMSC in cases with preoperative TMSC> 5 million/cc or 100% increase in TMSC in cases with preoperative TMSC< 5 million/cc. Patients were then categorized into two groups based on treatment success and statistical analysis was performed on these two groups

Statistical analysis

Statistical analysis was performed with IBM SPSS software version 19. T-test and Mann-Whitney U test were performed for parametric and non-parametric quantitative parameters and comparison was conducted by mean and standard deviation. Categorical variables were reported as the frequency with percentage. A comparison of these variables was performed by the chi-square test. Logistic regression and backward regression with a comparison of odds ratios were used for the identification of predictive factors of surgery outcomes and their approximate impact. Receiver operating characteristic (ROC) analysis and the Youden index were used for the detection of appropriate cut-off of variables. Experts' opinions were used for scoring of obtained factors. Afterward, the resultant scoring system and predictive model were tested on the present data of patients to ensure its accuracy and define its power for prediction. P-value cut-off of 0.05 was considered as the threshold for statistical significance.

Results

The population study consisted of 124 infertile patients with varicocele: 52 patients (41.93%) showed improvements in semen analysis after varicocelectomy (group 1) while the remaining 72 patients (58.06%) showed no response to varicocelectomy in terms of fertility parameters (group 2). Summary of demographic and hematologic variables are presented in Table 1. Parameters of semen analysis were checked before and after varicocelectomy. Nearly the findings are presented in Table 2. To determine the factors predicting outcomes

Table 3. *The area under the curve and cut-off analysis parameters*

Parameter	AUC	95% CI	p-value	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
BMI	0.783	0.703-0.863	0.000	23.70	79.2% (76.55-81.68%)	61.5% (58.40-64.53%)	67.29% (65.40-69.12%)	74.73% (72.18-77.11%)
NLR	0.808	0.716-0.899	0.000	1.80	87.5% (85.29-89.49%)	76.9% (74.16-79.48%)	79.11% (77.14-80.96%)	86.02% (83.88-87.91%)
Baseline TMSC	0.746	0.612-0.798	0.000	14.69	72.2% (69.31-74.96%)	76.9% (74.16-79.48%)	75.76% (73.50-77.89%)	73.45% (72.58-76.45%)

Table 4. *Predictive factors of varicocelectomy outcomes in multivariate analysis*

Parameter	Coefficient	Odds ratio	95% CI	p-value
BMI	2.37	2.7	2.27-50.44	0.003
NLR	3.19	3.4	4.77-124.24	0.000
Baseline TMSC	2.74	2.3	8.17-39.23	0.000

Table 5. *Scoring system for prediction of varicocelectomy outcomes*

BMI>23.70 kg/m^2 (4 scores)
NLR>1.80 (3 scores)
TMSC<14.69 million (2 scores)

of varicocelectomy, variables with a p-value of below 0.2 on univariate analysis were chosen for multivariate regression analysis. These variables included: age, BMI, platelets' count, NLR, PLR, baseline TMSC, and side. In multivariate analysis, BMI, NLR, and baseline TMSC remained significant. ROC analysis was also conducted for the detection of suitable cut-off of each variable for the prediction of postoperative outcomes. Cut-off values of 23.70 kg/m^2, 1.80, and 14.69 for BMI, NLR, and baseline TMSC were calculated, respectively. The details of the analysis of the area under cover (AUC), cut-off, sensitivity, and specificity of these factors are presented in Table 3. To formulate the predictive factors in a prediction model, multivariate analysis with calculation of odds ratio was performed. The details are shown in Table 4. To produce the final formula, the results of the multivariate analysis were used. Experts' opinions were also taken for giving each parameter a score in the formula. Finally, the obtained score was again tested on the data and the most sensitive and specific combination of scores for these parameters in the prediction of varicocelectomy outcomes were chosen. The resultant scoring formula is as follows (Table 5). ROC analysis of this score showed that a cut-off value of 5 is associated with an 87.5% sensitivity and an 84.6% specificity for prediction of failure of varicocelectomy in improving semen parameters and fertility. Figure 1 depicts the ROC curve for the suggested scoring system.

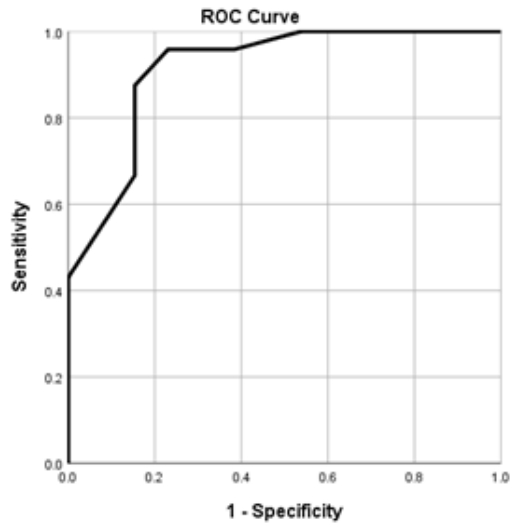

Fig 1. *ROC curve analysis of the scoring system*

Discussion

In our study, varicocelectomy improved semen parameters in nearly all patients but the degree of improvements vary between cases. In the efforts for finding the best infertile candidates for varicocelectomy, we concluded that three parameters of BMI, NLR, and baseline TMSC can be beneficial in predicting the impact of varicocelectomy on semen parameters. Thus, we formulated a scoring system for the appropriate selection of patients who will benefit the most from this surgery. We found that BMI was negatively associated with postoperative improvements in semen parameters. Interestingly, a recent meta-analysis has revealed that BMI is inversely associated with the occurrence of varicocele.[18] Additionally, it is reported that higher BMI is correlated with impaired semen parameters.[19] Given these findings, we can assume that patients with lower BMI, more frequently suffer from varicocele but will benefit from varicocelectomy more than obese people in terms of improving fertility measures. Consistent with our findings, Ates et al.[17] have also reported that postoperative improvements in semen parameters are better in patients with lower BMI. They also pointed out that BMI could independently predict the fertility outcomes of varicocelectomy. Albeit, it should be noted that there is no common agreement regarding the impact of BMI on postoperative fertility parameters in varicocelectomy. Chen et al.[20] have reported no impact of BMI on varicocelectomy outcomes. Pham et al. [21] have also reported similar results between different BMI groups. Shabana et al.[22] have also revealed insignificant

differences between responder and non-responders to varicocelectomy regarding semen parameters. It seems that larger clinical trials or meta-analysis studies are needed to clarify the role of BMI in post-varicocelectomy fertility function.

Total motile sperm count was another factor with a significant impact on varicocelectomy outcomes. Our findings indicate that higher baseline TMSC is associated with deeper improvements in semen parameters postoperatively. Consistent with our study, many previous studies in the literature have reported that varicocelectomy leads to significant improvements in TMSC with variations between different baseline TMSC groups.[23-27] A meta-analysis has reported that post-varicocelectomy TMSC had elevated by 10, 20, 15.77, 19.18, and 49.68 million in profound, severe, moderate, and mild degrees of TMSC, respectively.[28] Another study chose a cut-off value of 10 million for TMSC and reported that preoperative TMSC>10 is significantly associated with better semen changes compared to TMSC<10.[29] Thus, there is almost consensus among authors about the role of TMSC level and varicocelectomy success.

The Neutrophil-to-lymphocyte ratio was another factor implicated in our scoring system. NLR as an inflammatory indicator has been examined in various malignant conditions. NLR was proved to be a prognostic marker of urothelial markers, gastric cancer, hepatocellular cancer, pancreatic cancer, and breast cancer.[30-34] Studies have shown that higher levels of NLR have been associated with poorer outcomes in those conditions.[35] NLR has also been considered a determinant for morbidity and mortality in vascular disorders. For the first time in 2017, Mosmiller proposed that NLR can be used in the evaluation of chronic venous insufficiency.[36] Given the inflammatory and venous mechanisms involved in the pathogenesis of varicocele, Ates et al.[17] used NLR as a predictive factor for outcomes of varicocelectomy. They reported that NLR is a significant factor for the prediction of success of varicocelectomy (OR=3.6, $p<0.001$). Our study confirm the results obtained by Ates et al.[17] Thus, laboratory hematologic tests through calculation of NLR can be beneficial in planning the treatment of infertile men with varicocelectomy. However, main limitation of our study is the relatively short duration of follow-up. In longer periods of follow-up, real pregnancy rates could be determined. Larger sample sizes in future studies can produce results with higher levels of reproducibility and validity.

In conclusion, varicocelectomy can improve semen analysis parameters in almost all infertile men with varicocele. Using BMI, NLR, and baseline TMSC as the suggested scoring system can predict the success of varicocelectomy for improving fertility and determine the appropriate infertile candidates for varicocele surgery.

List of acronyms

BMI - Body mass index
CBC - Complete blood count
MPV - Mean platelet volume
NTR - Neutrophil to lymphocyte ratio
PDW - Platelet distribution width
PLR - Platelet to lymphocyte ratio
TMSC - Total motile sperm count
TTV - Total testicular volume
TVD - Testicular volume difference
WBC - White blood cells

Contributions of Authors

All five authors have approved the submitted and modified version of paper and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Conflict of Interest

There is no conflict of interest or any financial agreement with companies whose products may be alluded to in the paper.

Ethical Publication Statements

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

The authors declare that all material in this manuscript is our own work and all materials discussed within the text from other sources have been clearly referenced to the respective bibliography, in compliance with our understanding of the current definition of plagiarism.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Corresponding Author

Farshad Namdari, Aja University of Medical Sciences, Tehran, Iran. Etemadzadeh St, West Fatemi Ave, Tehran, 1411718541, Iran. Phone: +2188028350
ORCID iD: 0000-0002-4813-2665
E-mail: farshad.namd@yahoo.com

E-mails and ORCID iD of co-authors

Naser Yousefzadeh Kandevani: *naser.y.tums@gmail.com*
ORCID iD: 0000-0002-9945-0524
Morteza Hamidi: mortezahamidi1@yahoo.com
ORCID iD: 0000-0003-0981-5030
Hossein Dialameh: hossein.dialameh@gmail.com
ORCID iD: 0000-0002-8673-3664
Arya Behzadi: aryabehzadi1377@gmail.com
ORCID iD: 0000-0002-9927-8891

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