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ORIGINAL ARTICLE

Predictability of varicocele repair success: preliminary results of a machine learning-based approach

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Varicocele is a prevalent condition in the infertile male population. However, to date, which patients may benefit most from varicocele repair is still a matter of debate. The purpose of this study was to evaluate whether certain preintervention sperm parameters are predictive of successful varicocele repair, defined as an improvement in total motile sperm count (TMSC). We performed a retrospective study on 111 patients with varicocele who had undergone varicocele repair, collected from the Department of Endocrinology, Metabolic Diseases and Nutrition, University of Catania (Catania, Italy), and the Unit of Urology at the Selcuk University School of Medicine (Konya, Türkiye). The predictive analysis was conducted through the use of the Brain Project, an innovative tool that allows a complete and totally unbiased search of mathematical expressions that relate the object of study to the various parameters available. Varicocele repair was considered successful when TMSC increased by at least 50% of the preintervention value. For patients with preintervention TMSC below 5×10^6, improvement was considered clinically relevant when the increase exceeded 50% and the absolute TMSC value was $>5 \times 10^6$. From the preintervention TMSC alone, we found a model that predicts patients who appear to benefit little from varicocele repair with a sensitivity of 50.0% and a specificity of 81.8%. Varicocele grade and serum follicle-stimulating hormone (FSH) levels did not play a predictive role, but it should be noted that all patients enrolled in this study were selected with intermediate- or high-grade varicocele and normal FSH levels. In conclusion, preintervention TMSC is predictive of the success of varicocele repair in terms of TMSC improvement in patients with intermediate- or high-grade varicoceles and normal FSH levels.

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INTRODUCTION

Infertility is a global health problem of which the prevalence is reported to be steadily increasing. It is estimated that around 48.5 million couples are infertile and that 50% of them stem from a male factor.[1] One of the most studied causes of male infertility is varicocele. This is the dilation of the veins of the pampiniform plexus, which drains blood from the testis. Varicoceles have a high prevalence in the general population being present in about 15% of men. However, even more interesting is that it occurs in about 40% of patients with primary infertility and up to 80% of those seeking to initiate a second pregnancy.[2] However, given the high prevalence of varicocele in the general population, it can often be associated with other diseases,[3] unhealthy lifestyles,[4] and exposure to pollutants[5,6] that result in spermatogenic impairment. Therefore, to date, which patients would benefit most from varicocele repair is still debated, considering that only 20% of them have abnormal semen quality.[3] On these premises, a recent global survey involving 60 experts in the field of urology/andrology showed a wide divergence in their management of varicocele and in following the guidelines of scientific societies in clinical practice. This highlights the need for further studies investigating the more controversial aspects of varicocele management in infertile patients.[7]

Currently, it is believed that only patients with clinically palpable varicocele, a documented history of infertility for more than 1 year, and abnormal seminal parameter values should be treated.[8] However, there is still no consensus on which factors are predictive of response to varicocele repair. This is an old but still current and unsolved issue. Indeed, as early as 1986, a study observed that lack of testicular atrophy, a total sperm count $>50 \times 10^6$, sperm motility ≥60%, and serum follicle-stimulating hormone (FSH) values below 300 ng ml^{-1} were useful preoperative predictors of postoperative pregnancy rate.[9] Another study demonstrated that only normozoospermic, moderate oligozoospermic, and asthenozoospermic patients show benefits after treatment, while no significant improvement is observed in severely oligozoospermic patients.[10] Multiple regression models, devised to build predictive nomograms of responsiveness, found that the statistically significant predictors of improvement in sperm concentration after varicocele

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repair were left varicocele grade, sperm concentration, and sperm motility. Predictors of improvement in sperm motility after repair were age, left varicocele grade, preintervention motility, normal morphology, and total motile sperm count (TMSC). Predictors of improvement in sperm morphology after repair were age, right varicocele grade, preintervention normal morphology, and TMSC. Finally, predictors of TMSC increase after repair were the grade of left varicocele, ejaculate volume, preintervention sperm concentration, and preintervention sperm motility.[11] A recent study involving 124 patients with varicocele demonstrated, through logistic regression and backward regression, that body mass index, TMSC, and blood neutrophil-to-lymphocyte ratio can be predictive of postoperative improvement.[12]

In recent years, the use of machine learning methods has made it possible to generate algorithms capable of significantly improving the process of diagnosis, prognosis, outcome prediction, and treatment planning of various uro-andrological diseases. This is particularly true for prostate cancer, urolithiasis, renal cancer, and urothelial cancer.[13] However, its role in varicocele as a predictor of therapeutic success is poorly investigated. Indeed, to our knowledge, only one study has evaluated the role of a machine learning model (random forest) in predicting improvement in sperm parameters after varicocele repair, highlighting the importance of FSH and bilateral varicocele in predicting improvement.[14]

The Brain Project is an innovative tool that combines learning techniques (such as genetic programming) that implements a hybrid scheme derived from Darwinian evolution and artificial neural networks.[15,16] As already demonstrated in various application domains,[17,18] this combination of particular techniques allows a global and totally unbiased search of mathematical expressions that relate the object of study to the various available parameters (features). At the same time, it allows the identification, from all the features taken into consideration, the minimum number that provides the best predictive result. For example, a study that applied this methodology in the metabolic field showed that waist circumference and age are sufficient and simple predictive factors for screening dysglycemia with the same effectiveness as other methods that take into consideration a higher number of parameters.[17]

On this basis, in this preliminary study, we used the Brain Project to evaluate which preintervention parameter(s) play(s) a relevant role in predicting the success of varicocele repair. To our knowledge, this is the first time that evolutionary genetic algorithms have been applied to the study varicocele. On the basis of current literature,[12,19] successful varicocele repair is defined as an improvement in TMSC >50%, and in the case of preintervention TMSC $<5 \times 10^6$, an absolute value above than 5×10^6.

PATIENTS AND METHODS

Selection of patients

This study was conducted with the collaboration of the Department of Endocrinology, Metabolic Diseases and Nutrition, University of Catania (Catania, Italy), and the Unit of Urology at the Selcuk University School of Medicine (Konya, Türkiye). Data from patients with varicocele who were counseled during the period from January 2010 to December 2021 were reviewed retrospectively. The diagnosis of varicocele was initially formulated clinically through the study of the patients in orthostatism by clinicians experienced in the diagnosis of this condition. Specifically, according to the Dubin–Amelar classification, varicocele was classified as Grade I if detectable only during the Valsalva maneuver performed in orthostatism, Grade II if detectable even without the Valsalva maneuver, and Grade III if the varicocele was voluminous and already visible on scrotal inspection.[20] For the Italian population, the diagnosis was also confirmed by an echo-color Doppler ultrasound evaluation of the pampiniform plexus and the varicocele classified according to the Sarteschi classification, which is based on the diameter of the varices and the extent of the reflux.[21] Experienced andrologists trained in the ultrasound field performed both clinical and echo-color Doppler examinations.

All patients with left varicocele, independently of grade, who underwent varicocele repair by scleroembolization or surgical varicocelectomy were included, regardless of the reason of varicocele repair (*e.g.*, infertility, scrotal pain, *etc.*). The Italian cohort underwent varicocele repair by scleroembolization, while the Türkish cohort underwent microscopic subinguinal varicocelectomy. Patients with azoospermia, urogenital infections, chronic diseases, or hypogonaism were excluded.

The present study protocol was reviewed and approved by the Intra-divisional Ethics Committee of the Endocrinology, Metabolic and Nutritional Disease Section, Department of Clinical and Experimental Medicine, University of Catania (Approval No. 14/2022). Informed consent was obtained from all participants.

Collection of parameters and analysis of semen

Before varicocele repair, the values of the following parameters were collected: age, serum luteinizing hormone (LH), FSH, and total testosterone levels, conventional semen parameters (semen volume, sperm concentration, total sperm count, total and progressive motility, and normal forms), leukocyte concentration, laterality of varicocele (unilateral or bilateral), right, left, and mean testicular volume, grade of left and right (if present) varicocele, type of varicocele repair, and TMSC before varicocele repair.

Semen was analyzed after 3–5 days of sexual abstinence following the criteria published by the World Health Organization (WHO) in 2010.[22] Given the high intraindividual variability of sperm analysis, at least two examinations were performed before and after the varicocele repair, and in both cases, the better one (in term of semen quality and therefore of TMSC) of the two examinations was selected. Semen was examined 6 months after varicocele repair.

A patient's condition was considered as improved if there was at least a 50% increase in TMSC following varicocele repair.[12] For patients with preintervention TMSC $<5 \times 10^6$, improvement was considered clinically relevant if TMSC increased by at least 50% and reached an absolute value $>5 \times 10^6$, as this value has been reported to be associated with a greater chance of a spontaneous pregnancy.[19]

Description of the varicocele repair treatment

The surgical repair of the varicocele was performed by microscopic subinguinal varicocelectomy. Briefly, a 2–3 cm oblique skin incision was made over the external inguinal ring. The incision was deepened through the fascial layers of Camper and Scarpa and then the spermatic cord was grasped by a Babcock clamp. Subsequently, the testis was delivered, and the gubernacular veins and external spermatic perforators were isolated and dissected. The testis was repositioned in the scrotum, and the spermatic cord was elevated using a large Penrose drain. The microscope (Carl Zeiss Surgical GmbH, Oberkochen, Germany) was then introduced into the operative field, and the cord was examined at ×8 to ×15. A window was opened between the internal spermatic vessels and the external spermatic fascia to simplify the procedure and minimize the risk of injury to the vas deferens and its vessels during subsequent cord dissection. A thin tape was inserted between the internal spermatic vessels and the external spermatic fascia together with associated structures. The procedure was continued by dissecting the contents of the internal spermatic fascia. Once identified, micro-Doppler ultrasound was used to locate the artery, when the artery and a few (usually 2–5) lymphatic vessels were carefully separated from the surrounding veins and encircled with a 2-0 silk ligature for clear identification. All internal spermatic veins were ligated with 4-0 silk and subsequently divided. At the end of this initial dissection, the cord was stripped of its surrounding tissues, leaving only the identified artery (or arteries) and lymphatics intact. Subsequently, the contents of the external spermatic fascia were elevated and dissected. The vas deferens and their accompanying vessels were identified and preserved during this process. Furthermore, any cremasteric artery present was also safeguarded. The remaining cremasteric fibers and veins were ligated and effectively removed to expose the cord structure. At the end of the varicocelectomy procedure, the cord should consist only of the testicular artery (or arteries), the vas deferens, associated vessels, and lymphatic vessels of the spermatic cord.[23]

Sclerotherapy was performed by ultrasound-guided percutaneous access in the right common femoral or basilic vein until reaching the distal portion of the left spermatic vein. Once the distal catheterization was obtained, a diagnostic phlebography was performed according to the Bähren classification to study the presence of any collateral branch in the venous gonadal drainage.[24] After phlebography, an angioplasty balloon was advanced to the levels of the superior border of the left iliac bone and inflated to stop the retrograde flow. A second phlebography was performed to show previously unseen collaterals. Moreover, to prevent phlebitis, a rubber band was applied higher up the scrotum to prevent reflux of the sclerosant into the scrotal vein. At this point, atoxisclerol 3% (lauromacrogol 400 polidocanol; Chemische Fabrik Kreussler & Co. GmbH – Rheingaustrasse, Wiesbaden, Germany) was injected to perform sclerotherapy. If systemic collaterals were observed at phlebography, a mixture of contrast agent and sclerosant was injected until the proximal part of the collateral was seen. Finally, the occlusive balloon was deflated and a phlebographic control was performed.[25]

Brain Project model

We performed an extensive correlation search across all the features described in **Table 1** to predict improvement after varicocele repair on sperm parameter values using the Brain Project. The Brain Project is a new machine learning tool for nonlinear regression based on a hybridization of genetic programming and artificial neural networks that cooperate to obtain, in a fully automatic way, a solution to the proposed classification problem. It implements a well-known scheme based on the theory formulated by Charles Darwin a few centuries ago. Through the mechanism theorized by Darwin, an initial population evolves toward individuals whose characteristics are better adapted to the environment. Similarly, in the evolutionary computing, the Darwinian scheme is simulated to maximize a generic function called fitness. The latter numerically describes an individual's ability to adapt to the environment. Hence, for example, if we have predators in a snowy environment, the fitness values could be related to the skin color of the rabbits (the lighter the color, the higher its value). Genetic programming is an evolutionary algorithm where individuals in the population are mathematical functions. In our case, those functions represent the mathematical expressions of possible response to predictors of varicocele repair. The fitness function takes into account the predictive goodness, the complexity of the model, and the number of features considered in the final predictor formula.

Table 1: Characteristics of the patients included in this study (total=111)

Parameter	*Value*
Age (year), mean±s.d.	29.6±8.1
LH (mIU ml^{-1}), mean±s.d.	4.2±2.0
FSH (mIU ml^{-1}), mean±s.d.	4.8±3.0
TT (ng dl^{-1}), mean±s.d.	5.7±1.8
Seminal fluid volume (ml), mean±s.d.	3.3±1.5
Sperm concentration ($\times10^6$ ml^{-1}), mean±s.d.	22.8±27.5
Total sperm count ($\times10^6$ per ejaculate), mean±s.d.	66.7±79.3
Progressive sperm motility (%), mean±s.d.	21.3±13.4
Total sperm motility (%), mean±s.d.	51.1±15.1
Normal sperm morphology (%), mean±s.d.	5.4±4.5
Total motile sperm count ($\times10^6$), mean±s.d.	16.6±24.6
Leukocyte concentration ($\times10^6$ ml^{-1}), mean±s.d.	0.9±1.7
Monolateral varicocele (left only), *n* (%)	75 (67.6)
Bilateral varicocele, *n* (%)	36 (32.4)
Left varicocele degree according to Sarteschi's scale in Italian population, *n*/total (%)	
Grade I	0/91 (0)
Grade II	2/91 (2.2)
Grade III	27/91 (29.7)
Grade IV	59/91 (64.8)
Grade V	3/91 (3.3)
Right varicocele degree according to Sarteschi's scale in Italian, *n*/the number of patients with bilateral varicoceles (%)	
Grade I	2/35 (5.7)
Grade II	12/35 (34.3)
Grade III	10/35 (28.6)
Grade IV	11/35 (31.4)
Grade V	0/35 (0)
Left varicocele degree according to Dubin's scale in Türkish population, *n*/total (%)	
Grade I	0/20 (0)
Grade II	6/20 (30.0)
Grade III	14/20 (70.0)
Right varicocele according to Dubin's scale in Türkish population, *n*/the number of patients with bilateral varicoceles (%)	
Grade I	13/13 (100.0)
Grade II	0/13 (0)
Grade III	0/13 (0)
Right testicular volume (ml), mean±s.d.	15.0±3.6
Left testicular volume (ml), mean±s.d.	13.3±3.6
Mean testicular volume (ml), mean±s.d.	14.1±3.4
Type of intervention, *n* (%)	
Ligature	25 (22.5)
Scleroembolization	86 (77.5)

LH: luteinizing hormone; FSH: follicle-stimulating hormone; TT: total testosterone; s.d.: standard deviation

The average fitness of a population increases owing to the natural selection of individuals. Natural selection is the mechanism by which individuals with higher fitness are more likely to survive and generate new offspring than individuals with lower fitness. Thus, generation after generation, individuals have better predictive accuracy, lower complexity, and fewer features. The trade-off between prediction accuracy, model complexity, and number of features is user-definable. In this way, it is possible to develop different models, in each of which one or more of these aspects takes greater importance than the others. For further insight into the methodology, see studies of Russo.[15,16]

Statistical analyses

Quantitative variables are expressed as mean and standard deviation. Qualitative variables are presented as percentages. Considering the small number of patients, it was decided to employ 90% of the population for the learning phase and 10% for the testing phase. The assignment of patients to the two groups was done randomly. The Brain Project in the learning phase returns a mathematical formula consisting of nodes. The node represents any constant, variable, or mathematical function that is part of the formula. Application of the formula provides a continuous numerical value. A value near 0 represents that the patient does not improve, and a value near 1 represents that the patient does improve. Because the algorithm returns a continuous number, a threshold value was applied at 0.5 to distinguish patients identified by the algorithm as improved from those who did not improve. All patients for whom Brain Project formula returned a value ≤0.5 were considered as 0 and thus classified as unimproved; conversely, patients with a value >0.5 were considered as 1 and thus classified as improved. We also evaluated the correspondence between what the algorithm found and the actual outcome.

Moreover, the area under the receiver operating characteristic (ROC) curve (AUC) was calculated to evaluate the accuracy of the identified algorithm. To express the accuracy of the algorithm, the F1 index was calculated. It takes into account the precision and recovery of the test, where precision is the ratio between true positives and all positive results, and recovery is the ratio between true positives and all tests resulted as positive. F1 is the harmonic mean of precision and recovery.

Three-dimensional (3D) scatter was used to show the distribution of outcome in relation to TMSC and sperm concentration, total number, progressive motility, and normal forms of spermatozoa.

Finally, the predictive ability of the parameters identified by the Bain Project algorithm was validated by regression analysis, considering postoperative TMSC as the dependent variable and the other variables collected as independent variables.

Statistical analysis was performed with MedCalc Software (version 19.6–64-bit; MedCalc Software Ltd., Ostend, Belgium). $P < 0.05$ was considered statistically significant.

RESULTS

Data from 140 patients who underwent surgical varicocelectomy or scleroembolization were reviewed retrospectively. The data of interest were fully available in 111 patients, and, thus, used for our analysis. The features of the included patients are summarized in **Table 1**.

The data from 98 patients were used for the learning process and from 13 patients for the testing phase to validate the algorithm derived in the previous phase. The analysis, whose formula is Outcome = max (0.15091, −1.4213 × sin [0.82827 + tan (TMSC) + TMSC] × 0.9856^{TMSC}), identified a model with 13 nodes (threshold = 0.5) in the learning phase. This model, by selecting the TMSC values before varicocele repair, was able to predict patients with significant improvement, with a sensitivity of 60.6% and a specificity of 98.5%. The later phase of testing was less accurate but still able to identify patients with improvement correctly, with a sensitivity of 50.0% and a specificity of 81.8%. The ROC curve calculated on all patients confirmed a moderate accuracy of the algorithm (AUC = 0.726; **Figure 1**), as did the F1 index (0.7119).

Considering the entire population examined, 21 of the 24 patients (87.5%) identified by the algorithm as having improved actually had improved clinically. Similarly, 73 of the 87 (83.9%) patients identified by the algorithm as nonimproved showed no clinical improvement.

After several learning tests, we evaluated the current data set with lower complexity models. By setting the maximum number of nodes at 15, the Brain Project identified various models with a different number of features. In all cases, the model included preintervention TMSC values. Furthermore, from all models, only one with preintervention TMSC alone and 13 nodes performed approximately the same in terms of accuracy, sensitivity, and specificity as all the others. Thus, given a maximum number of 15 nodes, the model that performed best in terms of accuracy was that with 13 nodes and selected TMSC values before varicocele repair alone as a predictor of final outcome. Multivariate regression analysis confirmed that preintervention TMSC was the only variable that was independently correlated with TMSC postrepair (P = 0.0134; **Table 2**).

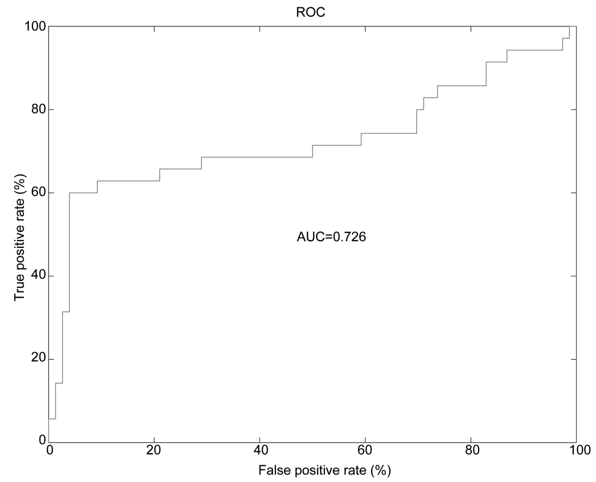

Figure 1: ROC curve showing the accuracy of the algorithm in predicting the outcome. ROC: receiver operating characteristic; AUC: area under the curve.

The algorithm failed to identify 14 of the 35 patients who would benefit from varicocele repair. The distribution of errors showed that they were clustered by low preintervention TMSC values (<10 × 10^6). However, in the context of low values of preintervention TMSC, when sperm concentration and total sperm count were considered, we found that the errors were more frequent for patients with TMSC <10 × 10^6 and sperm concentration values <10 × 10^6 ml^{-1} (**Figure 2a**) and total sperm count <40 × 10^6 (**Figure 2b**). Instead, there was no specific distribution of errors for changes in progressive motility (**Figure 2c**) or sperm morphology (**Figure 2d**).

DISCUSSION

In this study, we were able to identify by a machine learning-based approach the parameter that was more predictive of improved semen quality in varicocele patients undergoing repair. In particular, preintervention TMSC is sufficient to identify with sufficient accuracy those patients whose semen quality may not improve after varicocele repair. This finding clearly highlights how important preintervention TMSC is in predicting outcome in patients with varicocele. It also showed that preintervention TMSC appears to have all the information alone in this dataset analyzed in low-complexity models. Furthermore, the results of multivariate regression analysis confirmed and strengthened the results found by the Brain Project. This result agrees with those of a previous study, which identified TMSC as one of the predictive parameters of postvaricocelectomy improvement from logistic regression analysis.[12] A recent meta-analysis of six studies classified varicocele repair patients into four groups on the basis of preoperative TMSC levels (profound: <2 × 10^6, severe: 2 × 10^6–5 × 10^6, moderate: 5 × 10^6–10 × 10^6, and mild: >10 × 10^6). The study showed

Table 2: Regression analysis showing the relationship of postrepair total motile sperm count with the other collected parameters

Variable	*Coefficient*	*s.e.*	*t*	*P*	$r_{partial}$	$r_{semipartial}$
Postrepair TMSC	−5.0929					
Age	−0.7986	0.5318	−1.502	0.1375	−0.1743	0.1405
LH	−2.8961	2.3658	−1.224	0.2249	−0.1428	0.1145
FSH	0.7559	1.6117	0.469	0.6405	0.05519	0.04387
TT	0.2071	2.3575	0.0879	0.9302	0.01035	0.008218
Grade of left varicocele	11.0488	8.5738	1.289	0.2016	0.1501	0.1205
Grade of right varicocele	6.8963	7.8206	0.882	0.3808	0.1034	0.08248
Bilateral varicocele	−19.2762	22.6750	−0.850	0.3981	−0.09969	0.07951
Sperm volume	−1.9506	4.6632	−0.418	0.6770	−0.04924	0.03912
Sperm concentration	−0.2485	0.3996	−0.622	0.5359	−0.07310	0.05817
Total sperm count	−0.05316	0.1892	−0.281	0.7796	−0.03309	0.02628
Sperm progressive motility	−1.1698	0.6980	−1.676	0.0981	−0.1938	0.1567
Sperm total motility	0.3066	0.3921	0.782	0.4368	0.09177	0.07314
Sperm normal morphology	0.5250	1.1683	0.449	0.6545	0.05289	0.04203
Leukocyte concentration	1.1161	2.3533	0.474	0.6368	0.05580	0.04436
Pre-TMSC	1.5711	0.6196	2.536	0.0134*	0.2863	0.2372
Type of repair	−6.7694	17.3220	−0.391	0.6971	−0.04601	0.03655
Right testicular volume	0.5247	2.8690	0.183	0.8554	0.02155	0.01710
Left testicular volume	0.288	1.624	0.176	0.8605	0.02078	0.01650

LH: luteinizing hormone; FSH: follicle-stimulating hormone; TT: total testosterone; TMSC: total motile sperm count; s.e.: standard error; *$P<0.05$

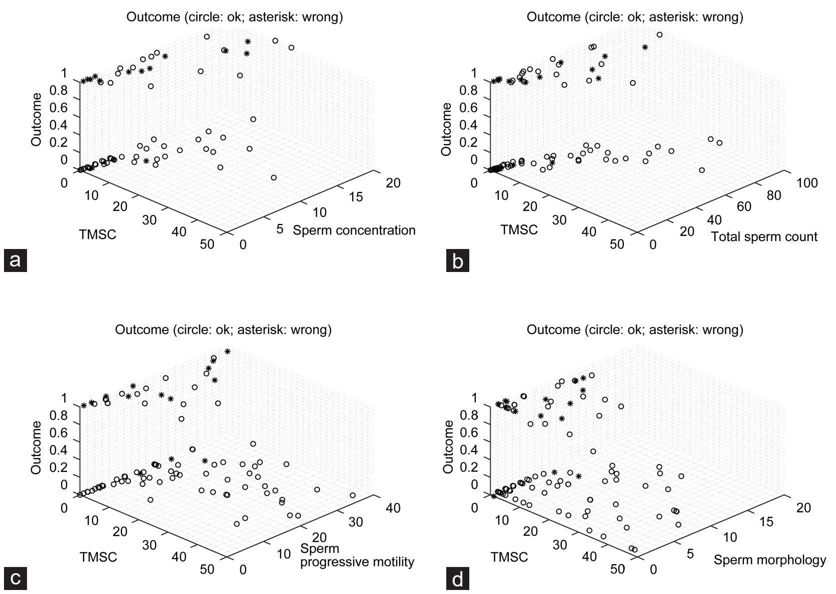

Figure 2: Graphs representing the distribution of errors committed by the Brain Project as a function of preintervention TMSC levels and (**a**) sperm concentration, (**b**) total sperm count, (**c**) sperm progressive motility, and (**d**) sperm morphology. Circle represented the patients whose outcome has been correctly identified by the algorithm; asterisks represented the patients whose outcome was not correctly identified by the algorithm. TMSC: total motile sperm count.

that, although varicocele repair was associated with improvement in TMSC in all groups, the one with the best quantitative benefit was that with mild impairment. Moreover, the partners of these patients also had the best spontaneous pregnancy rate after surgery, suggesting that TMSC is key for identifying patients who may benefit most from varicocele repair.[26] A recent study demonstrated and validated a nomogram, derived from data from varicocele patients treated with microsurgery, which showed initial TMSC as one of the predictors of the ability to achieve spontaneous pregnancy after varicocele repair.[27] It should be considered that TMSC, from its calculation, is strictly dependent on progressive sperm motility, suggesting that this parameter is essential to predict the success of varicocele repair. In fact, Shabana *et al.*[28] showed that preoperative progressive motility was important in predicting postoperative improvement in sperm parameter values for patients with Grade II or III clinical varicocele, identifying an 18% progressive motility threshold for distinguishing between responders and nonresponders. Another study conducted on 139 varicocele patients reported that sperm motility was a predictor of postoperative increase in sperm concentration by logistic regression analysis.[29] Furthermore, several studies have observed that preintervention progressive motility best predicts the possibility of achieving a spontaneous postintervention pregnancy, suggesting that this variable must be considered in the management of the patients undergoing varicocele repair.[30–32] The other parameter needed to calculate TMSC is the total sperm count. Therefore, a low TMSC, in addition to asthenozoospermia, may also be due to a low total sperm count. With this premise, it is well known that there is an inverse correlation between the severity of oligozoospermia and the risk of genetic abnormalities in patients who would benefit little from varicocele treatment.[33]

Interestingly, our evidence found that serum gonadotropin levels, particularly FSH, and varicocele degree were not key features in predicting improvement after varicocele repair. This is in contrast with several studies that have shown both FSH[9,13,14] and preintervention varicocele degree[11,28] to play an important predictive role. A probable explanation for this discrepancy is that all patients enrolled in our study had FSH levels within the normal range. Furthermore, almost all patients had varicoceles of intermediate or high degree according to the Dubin and Sarteschi classification; thus, a selection bias for both of these parameters could be present. Nevertheless, this allowed the identification of a parameter that predicts the response to varicocele repair in patients with normal FSH levels and intermediate/high-grade varicocele on at least one of the two sides.

This study used a machine-learning approach to analyze the predictability of improvement after varicocele repair. In another published study using such an approach, only FSH values, prerepair sperm concentration, and bilaterality were considered predictive parameters for postoperative sperm concentration improvement.[14] Moreover, in that study, the model predicted an improvement in 13 out of 39 patients and no improvement in 25 out of 47 patients. Furthermore, in our study, we found a high correspondence between what the algorithm predicts and what happens in real life, further strengthening the validity of the results. Therefore, our model has accuracy in line with and no worse than that found up to now in the literature, although it should be considered that the final outcome taken into consideration was different.[14]

In the present study, an increase in TMSC >50%, and in the case of preintervention TMSC $<5 \times 10^6$, an absolute value $>5 \times 10^6$, was considered a measure of the success of varicocele repair. We used TMSC because of its high predictive ability on pregnancy rate. In fact, it was observed that in patients with TMSC values $<5 \times 10^6$, the chances of spontaneous pregnancy are significantly reduced.[34] Moreover, TMSC value above 5×10^6 is associated with a higher success rate after intrauterine insemination.[35] Therefore, the evaluation of TMSC is a useful parameter for deciding which type of assisted reproductive technique is needed for infertile couples.[34] In addition, the predictive ability of TMSC has been confirmed by a large cohort study involving 1177 patients. The authors selected patients with male infertility as single diagnosis or unexplained infertility and followed them for a period of more than 3 years. The study showed that population grouping based on TMSC values had higher predictive accuracy on the possibility of achieving a spontaneous pregnancy than WHO classification. The cut-off of 5×10^6 TMSC differentiates patients with the best chance of pregnancy from those who would instead benefit from assisted reproductive techniques. Therefore, this parameter is correlated better with the severity of male infertility than the classification of patients according to sperm parameters suggested by the WHO manual on semen examination.[19,35] TMSC is also associated with a higher fertilization rate, lower abortion rate, and better embryo quality in intracytoplasmic sperm injection programs.[36]

This study has some limitations. First, the algorithm showed a low sensibility. However, we believe that this issue does not compromise the validity of the study. Indeed, a recent consensus has shown that clinicians often prescribe varicocele repair even in situations not suggested by guidelines, indicating a tendency to overtreat varicoceles.[7] In this sense, therefore, our algorithm, having a high specificity, would make it possible to identify those patients who would certainly not benefit from treatment, thus avoiding overtreatment. It is also necessary to improve the performance of the algorithm in terms of sensitivity, so as not to neglect patients who would instead benefit from repair. As noted, errors are primarily present with patients with low preintervention TMSC values due to low sperm concentration ($<10 \times 10^6$ ml^{-1}), indicating that other parameters may be needed to predict the success rate of repair in this specific category of varicocele patients. Second, the lower sensitivity and specificity rates in testing may suggest the possibility of overfitting. However, considering the low number of patients in the testing phase, even a single patient identified more or less correctly by the algorithm would significantly modify sensitivity and specificity. For this reason, it can still be assumed that the results are scientifically reasonable since learning and testing have a similar trend. Probably, as the complexity (number of nodes) of the model increases, other features could become important to improve the outcome. However, as has become apparent from our simulations, the dataset needs to be significantly increased to counteract the current overfitting problem that occurs when the maximum number of nodes is reached. Third, the study has a retrospective design, so it was not possible to preselect other features to be used for learning the Brain Project. Therefore, data collected prospectively could allow us to improve the quality of the results. Fourth, the sample size was small, so a larger population is needed to validate our algorithms and their possible predictive effectiveness. Finally, as we don't have data on the reproductive outcome of these patients' partners, we cannot tell whether the improvement in TMSC was reflected in the achievement of pregnancy.

Among the strengths of our article is the type of outcome chosen to evaluate of improvement. We did not choose the pregnancy rate, which is a composite outcome that takes into account the female partner, but selected a pure sperm parameter whose level is correlated with the pregnancy rate. As is usual for machine learning, the use of two patient populations allows a better generalization of the results.

CONCLUSIONS

Although with some limitations, our study suggests that for patients with intermediate- or high-grade varicocele and normal FSH levels, the values of TMSC before the repair, have an important predictive role for the improvement of TMSC after varicocele repair. The model could therefore be useful in identifying those patients who could benefit from varicocele repair. However, further studies with larger populations are needed to validate the model found in this study.

AUTHOR CONTRIBUTIONS

AC conceptualized the manuscript and was responsible for data curation, formal analysis, methodology, and writing original draft. MR was responsible for formal analysis and contributed to the review and editing of the text. AEC conceptualized the manuscript, was responsible of project administration, supervised the drafting of the article, and contributed to the review and editing of the text. VC contributed to data curation. MC and LMM contributed to data curation and methodology. RC was responsible for project administration and supervision and contributed to the review and editing of the text. SLV and RAC supervised, visualized, and validated the study. MG was responsible for data curation and visualized, and validated the final text. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

REFERENCES

1 Agarwal A, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the globe. *Reprod Biol Endocrinol* 2015; 13: 37.
2 Clavijo RI, Carrasquillo R, Ramasamy R. Varicoceles: prevalence and pathogenesis in adult men. *Fertil Steril* 2017; 108: 364–9.
3 Chiba K, Fujisawa M. Clinical outcomes of varicocele repair in infertile men: a review. *World J Mens Health* 2016; 34: 101–9.
4 Zampieri N, Zamboni C, Ottolenghi A, Camoglio FS. The role of lifestyle changing to improve the semen quality in patients with varicocele. *Minerva Urol Nefrol* 2008; 60: 199–204.
5 Calogero AE, Fiore M, Giacone F, Altomare M, Asero P, *et al*. Exposure to multiple metals/metalloids and human semen quality: a cross-sectional study. *Ecotoxicol Environ Saf* 2021; 215: 112165.
6 Cannarella R, Gül M, Rambhatla A, Agarwal A. Temporal decline of sperm concentration: role of endocrine disruptors. *Endocrine* 2023; 79: 1–16.
7 Shah R, Agarwal A, Kavoussi P, Rambhatla A, Saleh R, *et al*. Consensus and diversity in the management of varicocele for male infertility: results of a global practice survey and comparison with guidelines and recommendations. *World J Mens Health* 2023; 41: 164–97.
8 Jensen CF, Østergren P, Dupree JM, Ohl DA, Sønksen J, *et al*. Varicocele and male infertility. *Nat Rev Urol* 2017; 14: 523–33.
9 Marks JL, McMahon R, Lipshultz LI. Predictive parameters of successful varicocele repair. *J Urol* 1986; 136: 609–12.
10 Rodriguez Peña M, Alescio L, Russell A, Lourenco da Cunha J, Alzu G, *et al*. Predictors of improved seminal parameters and fertility after varicocele repair in young adults. *Andrologia* 2009; 41:277–81.
11 Samplaski MK, Yu C, Kattan MW, Lo KC, Grober ED, *et al*. Nomograms for predicting changes in semen parameters in infertile men after varicocele repair. *Fertil Steril* 2014; 102: 68–74.
12 Kandevani NY, Namdari F, Hamidi M, Dialameh H, Behzadi A. Developing a novel prediction model for the impact of varicocelectomy on postoperative fertility. *Eur J Transl Myol* 2022; 32: 10411.
13 Chen J, Remulla D, Nguyen JH, Dua A, Liu Y, *et al*. Current status of artificial intelligence applications in urology and their potential to influence clinical practice. *BJU Int* 2019; 124: 567–77.
14 Ory J, Tradewell MB, Blankstein U, Lima TF, Nackeeran S, *et al*. Artificial intelligence based machine learning models predict sperm parameter upgrading after varicocele repair: a multi-institutional analysis. *World J Mens Health* 2022; 40: 618–26.
15 Russo M. A distributed neuro-genetic programming tool. *Swarm Evol Comput* 2016; 27: 145–55.
16 Russo M. A novel technique to self-adapt parameters in parallel/distributed genetic programming. *Soft Comput* 2020; 24: 16885–94.
17 Buccheri E, Dell'Aquila D, Russo M. Artificial intelligence in health data analysis: the Darwinian evolution theory suggests an extremely simple and zero-cost large-scale screening tool for prediabetes and type 2 diabetes. *Diabetes Res Clin Pract* 2021; 174: 108722.
18 Dell'Aquila D, Gnoffo B, Lombardo I, Porto F, Russo M. Modeling heavy-ion fusion cross section data via a novel artificial intelligence approach. *J Phys G Nucl Part Phys* 2023; 50: 015101.
19 Hamilton JA, Cissen M, Brandes M, Smeenk JM, de Bruin JP, *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.
20 Dubin L, Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. *Fertil Steril* 1970; 21: 606–9.
21 Sarteschi M, Paoli R, Bianchini M, Fabris GFM, The echo-color-Doppler in the study of varicocele. *G Ital Ultrasonologia* 1993; 4: 43–9.
22 World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th ed. Geneva: World Health Organization; 2010.
23 Mirilas P, Mentessidou A. Microsurgical subinguinal varicocelectomy in children, adolescents, and adults: surgical anatomy and anatomically justified technique. *J Androl* 2012; 33: 338–49.
24 Bähren W, Biehl C, Danz B. Failed sclerotherapy trials with the V. spermatica interna. A retrospective analysis in 1141 patients with idiopathic varicocele. *Rofo* 1992; 157: 355–60.
25 Basile A, Failla G, La Vignera S, Condorelli RA, Calogero A, *et al*. Left spermatic vein retrograde sclerosis: comparison between sclerosant agent injection through a diagnostic catheter versus through an occluding balloon catheter. *Radiol Med* 2015; 120: 483–8.
26 Wang Q, Yu Y, Liu Y, Wang L. 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.
27 Liu L, Li J, Liu G, Pan C, Bai S, *et al*. Nomogram for predicting spontaneous pregnancy after microscopic varicocelectomy in infertile men with normal hormone. *BMC Pregnancy Child Birth* 2022; 22: 791.
28 Shabana W, Teleb M, Dawod T, Elsayed E, Desoky E, *et al*. Predictors of improvement in semen parameters after varicocelectomy for male subfertility: a prospective study. *Can Urol Assoc J* 2015; 9: E579–82.
29 Kiuchi H, Koga M, Hirai T, Namba Y, Takeyama M, *et al*. [Predictive factors associated with successful varicocele repair a study of 139 infertile men with valicocele]. *Nihon Hinyokika Gakkai Zasshi* 2005; 96: 480–6. [Article in Japanese]
30 Ren W, Qu J, Xue B, Hu J, Zu X. Infertility duration and pre-operative sperm progressive motility are significant factors of spontaneous pregnancy after varicocele repair. *Am J Reprod Immunol* 2020; 84: e13318.
31 Giagulli VA, Carbone MD. Varicocele correction for infertility: which patients to treat? *Int J Androl* 2011; 34: 236–41.
32 Pereira R, Sá R, Barros A, Sousa M. Major regulatory mechanisms involved in sperm motility. *Asian J Androl* 2017; 19: 5–14.
33 Krausz C, Riera-Escamilla A. Genetics of male infertility. *Nat Rev Urol* 2018; 15: 369–84.
34 Hajder M, Hajder E, Husic A. The effects of total motile sperm count on spontaneous pregnancy rate and pregnancy after IUI treatment in couples with male factor and unexplained infertility. *Med Arch* 2016; 70: 39–43.
35 Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, *et al*. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. *Fertil Steril* 2010; 93: 79–88.
36 Borges E Jr., Setti AS, Braga DP, Figueira RC, Iaconelli A Jr. Total motile sperm count has a superior predictive value over the WHO 2010 cut-off values for the outcomes of intracytoplasmic sperm injection cycles. *Andrology* 2016; 4: 880–6.