Original Article

The role of testicular stiffness derived from shear wave elastography in the assessment of spermatogenesis in men with varicocele

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Background: Varicocele is a major correctable cause of male infertility. Shear wave elastography (SWE) represents a valuable approach for assessing spermatogenesis in infertile men; however, its application in infertile men with varicocele remains unreported in the literature to date. The objective of this study was to investigate the correlation between testicular stiffness and spermatogenesis in individuals with varicocele.

Methods: A total of 568 participants with left-side varicocele and 475 age-matched healthy controls were enrolled. The mean, left, and right testicular volumes (Volume-mean, Volume-L, and Volume-R), the mean elastic modulus of bilateral, left, and right testes (Emean, Emean-L, and Emean-R); the maximum elastic modulus of bilateral, left, and right testes (Emax, Emax-L, and Emax-R); the minimum elastic modulus of bilateral, left, and right testes (Emin, Emin-L, and Emin-R) were calculated.

Results: Receiver operating characteristic (ROC) curves for Volume-R and Emax were constructed to identify participants with sperm concentrations below 5 million/mL. The areas under the ROC curves (AUCs) were 0.801 and 0.775, respectively. Combining these 2 markers improved their diagnostic value with an AUC of 0.820 and sensitivity and specificity of 94.6% and 59.8% [95% confidence interval (CI): 0.772–0.867, P<0.01], respectively. A total of 69 participants underwent microsurgical varicocelectomy (including 42 cases with improved semen results and 27 without). The ROC curves of Emax-L and Volume-L were constructed for the differential diagnosis between the improved and unimproved groups; the AUCs were 0.723 and 0.855, respectively. Combining these 2 markers improved their diagnostic value with an AUC of 0.867 (95% CI: 0.772–0.961, P<0.01) and sensitivity and specificity of 81.5% and 81.0%, respectively.

Conclusions: Our findings suggest that SWE can be used for varicocele to assess testicular parenchyma damage and Volume-L combined with Emax-L offers a more accurate method for predicting semen parameter improvement after microscopic subinguinal varicocelectomy in men with varicocele.

Keywords: Elasticity imaging techniques; male; testis; ultrasonography; varicocele

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Introduction

Varicocele is a major correctable cause of male infertility that is present in 15% of the male population, affecting 45% of men with primary infertility and 80% of men with secondary infertility (1). Despite the association between varicocele and male infertility, a large proportion of patients with varicocele remain fertile.

Ultrasound assessment of varicocele has focused on the size, duration, and velocity of regurgitation of the spermatic veins. However, no valid assessment tools have been found to evaluate histopathological changes in the testicular parenchyma in patients with varicocele.

Shear wave elastography (SWE) is a technique for noninvasively determining tissue stiffness quantitatively by measuring the velocity of the generated shear waves; the technique has reached maturity for diagnosing breast and thyroid tumors (2,3) and for assessing spermatogenic function in patients without varicocele (4,5). The use of SWE in varicocele testes has received much attention and is currently under active investigation. Studies have reported significant differences in SWE values between the ipsilateral testis with varicocele, the normal contralateral testis of the same patient, and the testis of healthy individuals. However, no correlation has been observed between testicular stiffness and varicocele grade (6,7). The findings of these studies are limited by their small sample sizes. Furthermore, the application of SWE in infertile men with varicocele has not been reported in the literature until now. Further studies using larger sample sizes are needed to confirm the feasibility and reliability of SWE in the routine evaluation of varicocele in infertile patients.

The indications for varicocelectomy in infertile patients are still debated. Some studies have shown improvements in semen quality, DNA fragmentation, and pregnancy rates after varicocele repair (8,9). However, other clinical investigations have reported unsatisfactory outcomes in infertile patients (10,11). To better determine the need for varicocelectomy, some clinicians assess varicocele grading, follicle-stimulating hormones levels, and semen results before surgery to predict treatment outcomes. Despite these considerations, some infertile men with clinical varicocele do not benefit from varicocelectomy (12). There is an urgent need for a more effective diagnostic strategy to identify patients who are likely to benefit from varicocelectomy.

In this study, we aimed to investigate the relationship between testicular stiffness and spermatogenic function in reproductive-aged men with varicocele through a large sample study. Additionally, we assessed the predictive value of SWE for semen improvement after macroscopic subinguinal varicocelectomy. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-8/rc).

Methods

Participant screening and enrollment

The present study protocol was reviewed and approved by the Institutional Review Board of Shengjing Hospital of China Medical University (Reg. No. 2018PS104J). Written informed consent was provided by all participants when they were enrolled. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Before commencing the study, we estimated the total study size to be 975 participants, allowing a power (1-abeta) of 95% at the 0.05 level of significance. Initially, a total of 2,543 consecutive participants who visited our Reproductive Medical Center from January 2018 to October 2022 were included. To reduce selection bias, strict inclusion and exclusion criteria were developed before the study.

The inclusion criteria were as follows: (I) left-sided varicocele diagnosed by gray-scale and color Doppler ultrasound; (II) testicular SWE was performed and satisfactory images were obtained; (III) semen analysis was performed within 7 days of the ultrasound.

The exclusion criteria were as follows: (I) abnormal semen results (including asthenozoospermia, teratozoospermia, asthenoteratozoospermia, oligozoospermia, and azoospermia) and no varicocele; (II) subclinical varicocele (ultrasound diagnosed varicocele but urologist could not detect it on palpation); (III) ultrasound findings affecting testicular stiffness, including testicular masses, extensive microlithiasis, hydrocele, cryptorchidism, solitary testis, and inguinal hernia; (IV) testicular biopsy within 3 months, history of testicular trauma, or urethral reconstruction surgery; (V) ejaculation disorders; (VI) obstructive azoospermia combined with varicocele; (VII) right-sided and bilateral varicocele; (VIII) failure to obtain satisfactory images for various reasons.

Ultrasound examinations

SWE was performed using a diagnostic ultrasound imaging system Aixplorer (SuperSonic Imagine, Aix-en-Provence, France) and a linear transducer with a frequency of 4–15 MHz. Scrotal ultrasonography and SWE were performed by an ultrasonographer with 6 years of testicular SWE experience.

The ultrasound examination was performed in the supine position. Gray-scale and color Doppler ultrasound of the scrotum and the inguinal region were performed. Varicocele was diagnosed using the scoring system published by Chiou *et al.* (13). This scoring system is a reliable diagnostic criterion and is most similar to palpation by a urologist.

The severity of varicocele was classified according to the method described by Dubin and Amelar (14). With the patient in a standing position, the presence of palpable spermatic veins when the patient was performing the Valsalva maneuver was classified as Grade 1, palpable spermatic veins at rest without a Valsalva maneuver was classified as Grade 2, and dilated veins visible through the scrotal skin was classified as Grade 3. Ultrasound-detected but non-palpable varicoceles were excluded from the analysis.

Testicular volume was calculated using Lambert's formula (testicular volume = length × width × height × 0.71) (15). The left and the right testicular volumes (Volume-L and Volume-R) were recorded separately, and the average volume of the bilateral testes was defined as the mean testicular volume (Volume-mean). The difference in volume between the left and the right testes was calculated and recorded as Volume-(R-L). The reduction percentage in Volume-L compared to Volume-R was calculated and recorded as volume-(R-L)/R.

For SWE imaging, all measurements were taken in the maximum longitudinal plane of the testis (*Figure 1*). The real-time SWE and gray-scale images were displayed simultaneously on the monitor. It displayed the elastic modulus with an SWE map in kPa (range, 0–180 kPa). A total of 3 consecutive measurements were taken and averaged at a 10 mm region of interest (ROI) in the middle of the testis, including the maximum elastic modulus, the mean elastic modulus, and the minimum elastic modulus. The mean values were recorded as the unilateral testicular elastic modulus, recorded as Emax-R, Emean-R, Emin-R, Emax-L, Emean-L, and Emin-L. The mean values of the bilateral testicular elastic modulus were recorded as the mean elastic modulus, including Emax, Emean, and Emin. If the testicular volume was small, the size of the ROI was adapted to the testicular volume.

Semen collection and analysis

After 3–7 days of abstinence, semen samples were collected by masturbation in the semen collection rooms and then assessed according to the guidelines established by the World Health Organization (WHO) in 2010 (16).

Patient grouping according to semen results

As procedures for the basic semen analysis in the 6th edition are consistent with the 5th edition, we divided participants into 5 groups based on semen results according to the WHO criteria for 2021 (WHO Laboratory Manual for the Examination and Processing of Human Semen, 6th edition) (17):

- Group I: normal control group, normozoospermia without varicocele (semen volume ≥1.4 mL, sperm concentration $\geq 16\times10^6$ /mL, progressive motility ≥30%, and normal form sperm morphology ≥4%);
- Group II: normozoospermia (semen standard is the same as Group I), with varicocele;
- Group III: asthenozoospermia, teratozoospermia, and asthenoteratozoospermia (semen volume ≥1.4 mL, sperm concentration $\geq 16\times10^6$/mL; progressive motility ≤30%, or progressive + non-progressive motility <42%, and/or normal form sperm morphology ≤4%), with varicocele;
- Group IV: oligozoospermia (sperm concentration $<16\times10^6$/mL), with varicocele;
- Group V: non-obstructive azoospermia (NOA), with varicocele.

Statistical analysis

Statistical analyses were performed using the software SPSS 25.0 (IBM Corp., Armonk, NY, USA). All data were first tested for normality using the Kolmogorov-Smirnov normality test. Data did not conform to a normal distribution, and were expressed as median and first and third quartiles. Statistical differences between 3 or more groups were determined using the Kruskal-Wallis test. Differences between paired samples were examined using Wilcoxon-matched pairs test. Linear regression analysis was performed, and Spearman rank correlation coefficients were calculated to determine the correlation between sperm concentration and testicular volume or testicular elastic modulus. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic performance of the testicular elastic modulus and volume-related parameters. The areas under the ROC curves (AUCs), sensitivities, and specificities were calculated and cut-off values were determined by Youden's index. Multi-indicator

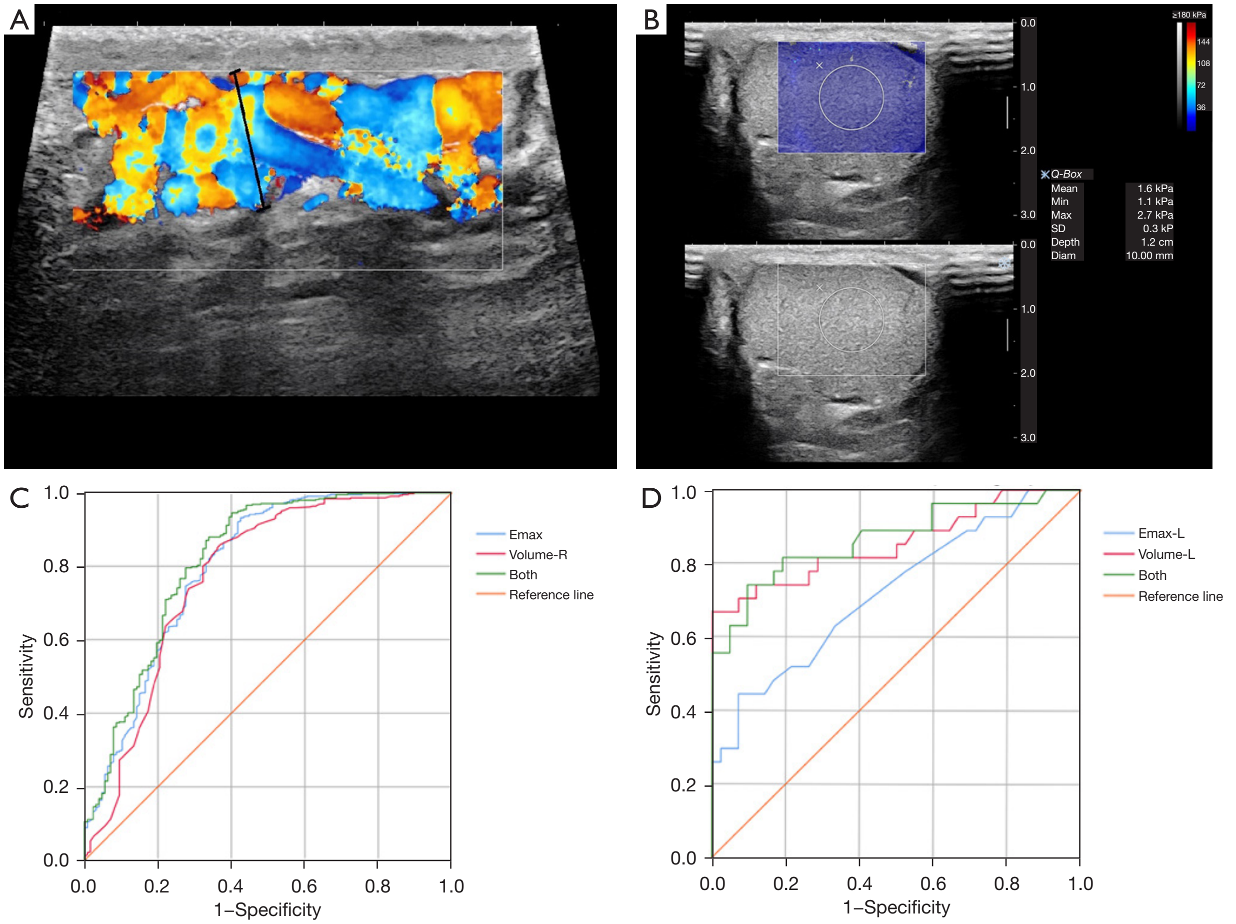

Figure 1 Color Doppler flow map of varicosed veins and SWE map of testicular parenchyma and ROC curves. (A) The 2-dimensional color Doppler flow map of venous plexus; The black line "I" represents the diameter of the pampiniform veins plexus; (B) the measurement of SWE is conducted on the maximum longitudinal plane in the middle of testis with a 10 mm ROI; (C) ROC curves of Emax, Volume-R, and combined marker in identifying participants with sperm concentration below 5 million/mL; (D) ROC curves of Emax-L, Volume-L, and combined marker in differential diagnosis between the improved and unimproved groups after varicocelectomy. SD, standard deviation; ROC, receiver operating characteristic; SWE, shear wave elastography; ROI, region of interest; Emax, maximum elastic modulus; Volume-R, the right testicular volume; Emax-L, maximum elastic modulus of the left testis; Volume-L, the left testicular volume.

combination ROC curves were constructed to evaluate the combined diagnostic performance of 2 indicators. A P value <0.05 indicated a statistically significant difference.

Results

Participant screening and enrollment

The flow chart of participant screening and enrollment is illustrated in *Figure 2*. A total of 1,500 cases were excluded due to violation of inclusion/exclusion criteria, leaving 1,043 participants for the final analysis, including 568 patients with left-side varicocele and 475 healthy individuals who required *in vitro* fertilization due to wife-related problems as a control group.

Age, sperm concentration, testicular volume-related parameters, and elastic modulus in different grades of varicocele (*Table 1*).

Differences in sperm concentration (P<0.05); Volume-mean, Emax, and Emax-R (P<0.01) were found in different grades of varicocele, but there was a significant overlap. Age, Volume-L, Volume-R, Volume-(R-L), Volume-(R-L)/R, Emax-L, Emean, Emean-L, Emean-R, Emin, Emin-L, and Emin-R had no statistically significant difference in

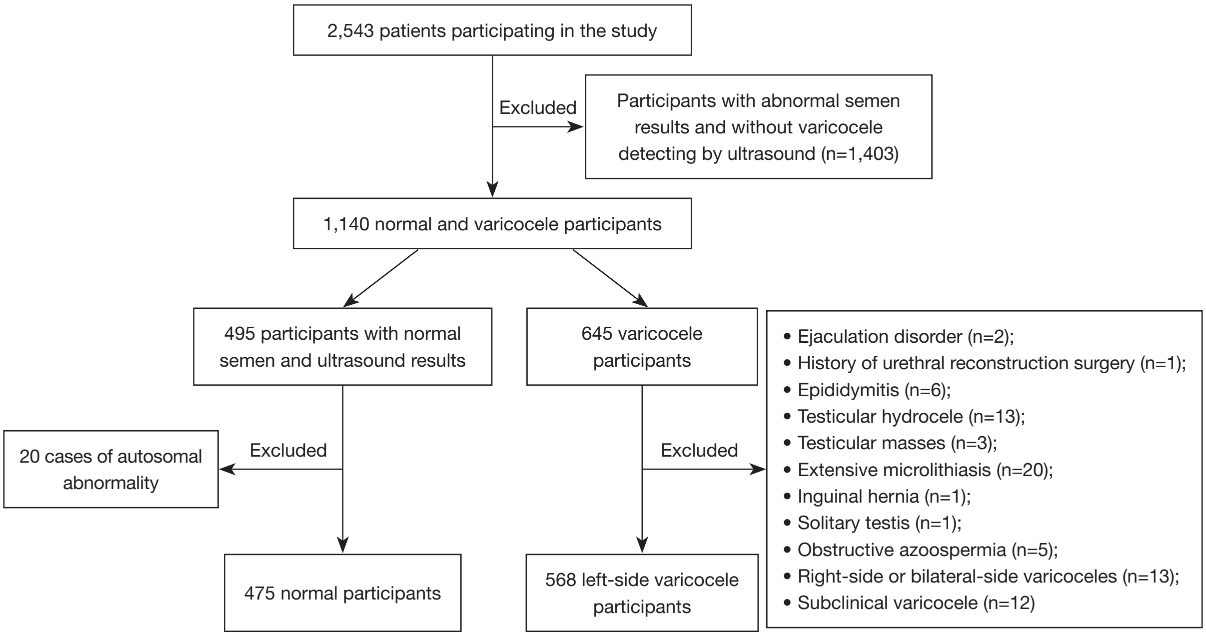

Figure 2 The flow chart of participant screening and enrollment.

Table 1 The ages, sperm concentrations, testicular volumes, and elastic modulus of different varicocele grades

Item	Grade 1 (n=195)	Grade 2 (n=229)	Grade 3 (n=144)	P value
Age (years)	32.00 (29.00, 36.00)	33.00 (30.00, 36.50)	32.00 (29.00, 36.00)	0.376
Sperm concentration (million/mL)	33.71 (9.98, 61.08)	23.91 (5.21, 48.80)	29.30 (5.67, 53.82)	<0.05
Volume-mean (mL)	9.97 (1.90, 14.27)	9.93 (2.00, 13.91)	11.99 (8.52, 15.02)	<0.01
Volume-L (mL)	12.81 (9.93, 15.27)	12.78 (9.30, 15.06)	12.30 (9.83, 15.45)	0.823
Volume-R (mL)	13.60 (10.48, 16.12)	13.42 (10.33, 15.68)	13.63 (11.03, 16.59)	0.570
Volume-(R-L) (mL)	0.81 (−0.24, 1.89)	0.69 (−0.42, 1.72)	0.93 (−0.47, 2.39)	0.250
Volume-(R-L)/R (%)	5.99 (−1.76, 14.12)	5.89 (−3.46, 12.86)	8.36 (−4.25, 16.85)	0.419
Emean (kPa)	1.75 (1.55, 2.00)	1.80 (1.58, 2.08)	1.75 (1.60, 1.95)	0.215
Emean-L (kPa)	1.70 (1.60, 2.00)	1.80 (1.50, 2.20)	1.70 (1.50, 2.00)	0.138
Emean-R (kPa)	1.70 (1.50, 2.00)	1.80 (1.60, 2.05)	1.80 (1.60, 2.00)	0.185
Emin (kPa)	1.10 (0.90, 1.30)	1.10 (0.90, 1.40)	1.10 (0.85, 1.30)	0.368
Emin-L (kPa)	1.10 (0.90, 1.40)	1.10 (0.80, 1.40)	1.10 (0.83, 1.30)	0.276
Emin-R (kPa)	1.10 (0.90, 1.40)	1.20 (0.90, 1.40)	1.10 (0.90, 1.30)	0.294
Emax (kPa)	2.75 (2.45, 3.40)	2.95 (2.60, 3.70)	3.00 (2.60, 3.74)	<0.01
Emax-L (kPa)	2.80 (2.50, 3.40)	2.90 (2.60, 3.80)	3.00 (2.60, 3.58)	0.144
Emax-R (kPa)	2.70 (2.40, 3.30)	2.90 (2.50, 3.60)	3.10 (2.60, 3.80)	<0.01

Data are represented as median (IQR). Varicocele grade: Grade 1, the presence of palpable spermatic veins when the patient was performing the Valsalva maneuver; Grade 2, palpable spermatic veins at rest without a Valsalva maneuver; Grade 3, dilated veins visible through the scrotal skin. Volume-mean, the mean volume of bilateral testes; Volume-L, the left testicular volume; Volume-R, the right testicular volume; Emean, mean elastic modulus; Emean-L, mean elastic modulus of the left testis; Emean-R, mean elastic modulus of the right testis; Emin, minimum elastic modulus; Emin-L, minimum elastic modulus of the left testis; Emin-R, minimum elastic modulus of the right testis; Emax, maximum elastic modulus; Emax-L, maximum elastic modulus of the left testis; Emax-R, maximum elastic modulus of the right testis; IQR, interquartile range.

Table 2 The ages, testicular volumes, and elastic modulus of different semen groups

Item	Group I (n=475)	Group II (n=147)	Group III (n=232)	Group IV (n=125)	Group V (n=64)	P value
Age (years)	32 (29.00, 35.00)	32.00 (29.00, 35.00)	33.00 (30.00, 37.00)	32.00 (29.00, 36.00)	32.50 (29.00, 35.00)	<0.01
Volume-mean (mL)	14.26 (11.92, 16.19)	14.38 (12.21, 16.22)	13.97 (11.55, 16.25)	11.90 (9.06, 14.32)	6.66 (5.05, 9.87)	<0.01
Volume-L (mL)	13.96 (11.66, 16.24)	14.06 (11.66, 15.84)	13.49 (11.16, 16.10)	11.66 (8.47, 13.85)	6.71 (4.33, 8.86)	<0.01
Volume-R (mL)	14.40 (12.07, 16.87)	14.84 (12.63, 16.62)	14.16 (11.96, 16.90)	12.05 (9.28, 14.81)	6.21 (4.93, 9.33)	<0.01
Emean (kPa)	1.70 (1.55, 1.95)	1.75 (1.60, 1.95)	1.75 (1.51, 1.95)	1.80 (1.65, 2.05)	2.00 (1.70, 2.35)	<0.01
Emean-L (kPa)	1.70 (1.50, 2.00)	1.70 (1.50, 2.00)	1.70 (1.50, 2.00)	1.80 (1.60, 2.10)	2.00 (1.60, 2.40)	<0.01
Emean-R (kPa)	1.70 (1.50, 2.00)	1.80 (1.60, 2.00)	1.70 (1.50, 2.00)	1.80 (1.55, 2.10)	2.00 (1.60, 2.30)	<0.01
Emin (kPa)	1.15 (1.00, 1.40)	1.15 (1.00, 1.40)	1.10 (0.90, 1.34)	1.10 (0.90, 1.30)	0.85 (0.65, 1.15)	<0.01
Emin-L (kPa)	1.20 (1.00, 1.40)	1.20 (1.00, 1.40)	1.10 (0.90, 1.40)	1.10 (0.85, 1.30)	0.80 (0.60, 1.18)	<0.01
Emin-R (kPa)	1.20 (0.90, 1.40)	1.20 (1.00, 1.40)	1.10 (0.90, 1.40)	1.10 (0.90, 1.30)	0.90 (0.70, 1.20)	<0.01
Emax (kPa)	2.65 (2.45, 2.90)	2.75 (2.45, 3.10)	2.80 (2.50, 3.19)	3.30 (2.70, 4.00)	4.45 (3.28, 6.54)	<0.01
Emax-L (kPa)	2.70 (2.40, 3.00)	2.70 (2.40, 3.10)	2.80 (2.50, 3.20)	3.20 (2.60, 4.10)	4.50 (3.08, 6.75)	<0.01
Emax-R (kPa)	2.70 (2.40, 3.00)	2.70 (2.40, 3.10)	2.70 (2.40, 3.20)	3.20 (2.70, 4.20)	4.60 (3.33, 6.50)	<0.01

Data are represented as median (IQR). Group I, normal controls; Group II, varicocele participants with normozoospermia; Group III, varicocele participants with asthenozoospermia, teratozoospermia and asthenoteratozoospermia; Group IV, varicocele participants with oligozoospermia; Group V, varicocele participants with non-obstructive azoospermia. Volume-mean, the mean volume of bilateral testes; Volume-L, the left testicular volume; Volume-R, the right testicular volume; Emean, mean elastic modulus; Emean-L, mean elastic modulus of the left testis; Emean-R, mean elastic modulus of the right testis; Emin, minimum elastic modulus; Emin-L, minimum elastic modulus of the left testis; Emin-R, minimum elastic modulus of the right testis; Emax, maximum elastic modulus; Emax-L, maximum elastic modulus of the left testis; Emax-R, maximum elastic modulus of the right testis; IQR, interquartile range.

different grades of varicocele (P>0.05).

There was no significant difference in the elastic modulus of bilateral testes in each grade of varicocele (P>0.05), and Volume-L was significantly smaller than Volume-R in all grades of varicocele (P<0.01).

Age, testicular volume-related parameters, and elastic modulus of varicocele participants in different semen groups (*Table 2*)

There were significant differences of age, Emean, Emean-L, Emean-R, Emax, Emax-L, Emax-R, Emin, Emin-L, Emin-R, Volume-mean, Volume-L, and Volume-R among different semen groups (P<0.01).

Sperm concentration was positively correlated with Volume-mean, Volume-L, and Volume-R with correlation coefficients of 0.287, 0.474, and 0.490, respectively (P<0.01). Sperm concentration was negatively correlated with Emax, Emax-L, and Emax-R with correlation coefficients of −0.392, −0.349, and −0.380, respectively (P<0.01). Sperm concentration was negatively correlated with Emean with a correlation coefficient of −0.120 (P<0.01). Sperm concentration was negatively correlated with Emean-L and Emean-R with correlation coefficients of −0.086 and −0.107 (P<0.05), respectively. Sperm concentration was positively correlated with Emin, Emin-L, and Emin-R, with correlation coefficients of 0.183, 0.184, and 0.150, respectively (P<0.01).

ROC curves of testicular volume-related parameters and elastic modulus in identifying sperm concentration below 5 million/mL (*Figure 1*).

Since Volume-R and Emax were strongly correlated with semen outcomes, we constructed ROC curves for Volume-R and Emax to identify participants with sperm concentrations below 5 million/mL (18) with AUCs of 0.801 [95% confidence interval (CI): 0.751–0.850, P<0.01] and 0.775 (95% CI: 0.721–0.829, P<0.01) (P<0.01), respectively. The cutoff value was obtained when the Youden index reached its maximum value. When the cutoff value of Volume-R was 9.69 mL, the sensitivity and specificity were 92.1% and 58.3%, respectively. When the cutoff value of Emax was 3.175 kPa, the sensitivity and specificity were 71.7% and 73.9%, respectively. Combining the 2 markers improved their diagnostic value with an AUC of 0.820 (95%

Table 3 Comparisons of ages, sperm concentrations, volume-related parameters, and elastic modulus between postoperative improved and unimproved groups after microsurgical varicocelectomy

Item	Improved group (n=42)	Unimproved group (n=27)	P value
Age (years)	30.00 (29.00, 35.00)	31.00 (29.00, 34.00)	0.490
Sperm concentration (million/mL)	31.81 (20.61, 47.49)	18.42 (0.00, 38.53)	<0.05
Volume-mean (mL)	14.93 (12.65, 17.63)	11.01 (5.75, 14.38)	<0.01
Volume-L (mL)	14.79 (11.87, 17.61)	9.50 (5.77, 11.96)	<0.01
Volume-R (mL)	14.92 (12.65, 17.92)	10.83 (5.75, 14.38)	<0.01
Emean (kPa)	1.80 (1.55, 2.11)	1.85 (1.60, 2.30)	0.313
Emean-L (kPa)	1.75 (1.50, 2.30)	1.70 (1.50, 2.40)	0.550
Emean-R (kPa)	1.75 (1.50, 2.03)	2.00 (1.60, 2.30)	0.214
Emin (kPa)	1.20 (0.94, 1.45)	1.10 (0.95, 1.65)	0.990
Emin-L (kPa)	1.15 (0.90, 1.60)	1.00 (0.80, 1.50)	0.702
Emin-R (kPa)	1.10 (0.90, 1.33)	1.20 (0.80, 1.60)	0.739
Emax (kPa)	2.78 (2.50, 3.10)	3.35 (2.75, 4.00)	<0.01
Emax-L (kPa)	2.70 (2.30, 3.30)	3.40 (2.70, 4.50)	<0.01
Emax-R (kPa)	2.70 (2.40, 3.23)	3.30 (2.60, 3.80)	<0.01

Data are represented as median (IQR). Volume-mean, the mean volume of bilateral testes; Volume-L, the left testicular volume; Volume-R, the right testicular volume; Emean, mean elastic modulus; Emean-L, mean elastic modulus of the left testis; Emean-R, mean elastic modulus of the right testis; Emin, minimum elastic modulus; Emin-L, minimum elastic modulus of the left testis; Emin-R, minimum elastic modulus of the right testis; Emax, maximum elastic modulus; Emax-L, maximum elastic modulus of the left testis; Emax-R, maximum elastic modulus of the right testis; IQR, interquartile range.

CI: 0.772–0.867, P<0.01) and sensitivity and specificity of 94.6% and 59.8%, respectively.

Comparisons of age, sperm concentration, testicular volume-related parameters, and elastic modulus between the postoperative improved and unimproved groups of microscopic subinguinal varicocelectomy (*Table 3*).

A total of 69 participants with varicocele underwent microscopic subinguinal varicocelectomy. Including 49 patients with asthenozoospermia, 13 with oligozoospermia, and 7 with non-obstructive azoospermia. Improvements in semen results can be defined if semen concentration or motility improves by more than 20% after surgery or the presence of spermatozoa in the ejaculate of azoospermic patients. Of these participants, 42 showed improvement in semen results at 3–6 months postoperatively (including 9 patients with asthenozoospermia and 33 with oligozoospermia) and 27 (including 4 patients with asthenozoospermia, 16 with oligozoospermia, and 7 with non-obstructive azoospermia) showed no significant improvement. We recorded the preoperative semen parameters of the participants.

Volume-mean, Volume-L, and Volume-R were significantly greater in the improved group than in the unimproved group (P<0.01). Emax, Emax-L, and Emax-R were higher in the unimproved group than in the improved group (P<0.01). There was no significant difference for the age, Emean, Emean-L, Emean-R, Emin, Emin-L, and Emin-R between the improved and unimproved groups (P>0.05).

ROC curves for Emax, Emax-L, Emax-R, Volume-mean, Volume-L, and Volume-R were constructed for the differential diagnosis of the improved and unimproved groups after microscopic subinguinal varicocelectomy (*Figure 1*). The AUCs were 0.714, 0.723, 0.687, 0.770, 0.855, and 0.749 (P<0.01). The highest predictive values were found for Emax-L (AUC =0.723, 95% CI: 0.599–0.847, P<0.01) and Volume-L (AUC =0.855, 95% CI: 0.755–0.955, P<0.01). The cutoff value was obtained when the Youden index reaches its maximum value. When the cutoff value of Emax-L was 3.45 kPa, its sensitivity and specificity were 48.1% and 83.3%, respectively. The sensitivity and specificity were 100% and 66.7%, respectively, when the cut-off value of Volume-L was 10.335 mL. Combining the 2 markers improved their diagnostic value with an AUC of 0.867 (95% CI: 0.772–0.961, P<0.01); sensitivity and specificity were 81.5% and 81.0%, respectively.

Discussion

In our study, the assessment of varicocele severity was initially classified using the Dubin and Amelar varicocele grading system, which is considered the gold standard for diagnosing clinically significant varicoceles and provides clear indications for varicocelectomy (19,20). However, upon further analysis, we identified certain limitations associated with this grading system. Firstly, no differences in sperm concentration were observed among different grades of varicocele. Secondly, testicular volume exhibited a significant association with semen volume, sperm count, and motility; it could serve as an indicator of men's reproductive reserve capacity. Sperm parameters in infertile men tend to deteriorate as testicular volume decreases (21). Nevertheless, we did not find any variations in testicular volume-related parameters across different grades of varicocele. Lastly, testicular elastic modulus can reflect parenchymal damage within the testes (5,18,22). Surprisingly though, no disparities were found in testicular elastic modulus among different grades of varicocele. Consequently, the Dubin and Amelar classification does not contribute significantly to diagnosing or making treatment decisions for infertile patients with varicoceles. Furthermore, the impact of varying degrees of varicocele on improvements in semen quality following surgical repair remains unclear (23,24).

For all the above reasons, we attempted to find other indicators closely related to testicular spermatogenesis to evaluate the severity of varicocele in infertile men. We grouped all participants according to their semen results and found that testicular volume-related parameters and elastic modulus were significantly different between semen groups. Testicular volume and elastic modulus reflect the severity of varicocele in terms of testicular spermatogenesis and are better indicators for assessing infertile varicocele patients.

Histopathological findings in testes with impaired spermatogenesis are characterized by fibrous thickening of the wall of the seminiferous tubules (25), which may lead to increased testicular stiffness, and SWE can reflect spermatogenic function by measuring testicular stiffness. Studies have shown that the elastic modulus correlates closely with sperm concentration and motility and is of high diagnostic value in assessing severe spermatogenic dysfunction (18,22). Erdogan *et al.* found that SWE could be a useful technique for assessing testicular stiffness in patients with varicocele and for predicting the severity of testicular parenchyma damage (6). Fuschi *et al.* performed testicular biopsies and SWE in patients with varicocele during and 6 months after varicocelectomy. The SWE results were consistent with postoperative histopathological changes, showing a decrease in testicular stiffness (26). In this study, we also found that testicular elastic modulus and testicular volume were closely related to sperm concentration in patients with varicocele. In addition, SWE was easy to perform and could be added to the routine ultrasound procedure. It is an appropriate diagnostic method for assessing spermatogenic function in infertile men with varicocele.

Mutations and genotypes in genes that regulate sperm production may cause male infertility (27). Microdeletions in the AZF region of the Y chromosome and a significantly increased incidence of autosomal abnormalities are only seen in infertile men with sperm concentrations below 5 million/mL (18). Semen analysis is a widely accepted method of assessing the spermatogenic function of the testes. However, the results of multiple semen analyses in the same individual may not be the same. This may be due to the length of abstinence or seasonal reasons, variations in the method of analysis, and inherent biological variability (28). A single sample is not sufficient to assess any abnormality in the semen results (29). In contrast, testicular elastic modulus and volume can reflect testicular parenchymal damage in real-time and are more stable than semen results. To this end, we used ROC curves to analyze the diagnostic ability of Volume-R and Emax in identifying participants with sperm concentrations less than 5 million/mL. Volume-R combined with Emax had a high sensitivity of 94.6% and was suitable for screening patients who require chromosomal analysis.

A number of sonographic classifications have been proposed to establish clear criteria for the diagnosis, treatment, and prognosis of varicocele. When adopting Chiou's ultrasound diagnostic system, we carefully considered various aspects. Firstly, all parameters of Chiou's system are evaluated with the patient lying supine, which aligns perfectly with our research methodology. Secondly, in our study, the severity of varicocele was classified according to Dubin and Amelar's method—the only classification system recognized by guidelines that is based on clinicians' palpation findings. However, Chiou's system takes into account both morphological and Doppler parameters of spermatic veins as well as considers the diameter of the spermatic venous plexus, making it unique among evaluation systems. Through extensive clinical practice, we have found that there is a stronger correlation between clinicians' palpation and Chiou's system. Considering these factors mentioned above, we decided to adopt Chiou's system for ultrasound diagnosis of varicocele.

In our study, we employed Chiou's ultrasound-based system for the diagnosis of varicocele and utilized Dubin and Amelar's clinical palpation-based classification to grade its severity. Although these 2 evaluation methods exhibit a strong correlation, our analysis identified 12 patients with very mild varicocele that could only be detected and diagnosed through ultrasound imaging rather than clinical palpation. We categorized these patients as having subclinical varicocele and excluded them from the statistical analysis due to their limited representation.

In the current European Association of Urology (EAU), the American Urological Association (AUA), and the American Society for Reproductive Medicine (ASRM) guidelines, the main indications for varicocelectomy in infertile men have been focused on men with poor semen quality and normal female partners (19,30,31). However, National Institute for Health and Clinical Excellence (NICE) guidelines state that varicocelectomy should not be used as part of infertility treatment because there is no evidence that varicocelectomy improves conception rates (32). Operative indications for varicocele currently remain controversial. There is an urgent need to improve the indications for varicocelectomy in infertile men. In this study, 69 (69/568) participants underwent microscopic subinguinal varicocelectomy. The differences of preoperative parameters between the improved and unimproved groups were analyzed. The improved group had significantly larger testicular volume and lower testicular stiffness compared to the unimproved group. Emax combined with Volume-L had high diagnostic value in predicting improvement in patients after varicocelectomy, with an AUC of 0.867 and sensitivity and specificity of 81.5% and 81.0%, respectively.

The strength of this study lies in its large sample size. However, our study also has some disadvantages. Firstly, it would be unethical to obtain testicular tissue from participants with varicocele for research purposes. Therefore, histopathological findings of the testes were not available in our study. Secondly, we did not calculate interobserver variability because only one operator did all the examinations. Thirdly, only cases presenting with left varicocele were included in this study, whereas those exhibiting right varicocele, bilateral varicocele, and subclinical varicocele were excluded, thereby limiting its generalizability to a broader population. Finally, significant female factors warranting *in vitro* fertilization may preclude the need for varicocele repair. Despite the large number of varicocele patients seen at our Center for Assisted Reproduction, very few patients are eligible for varicocele repair surgery; further large-sample, multicenter studies are needed.

Conclusions

Volume-R combined with Emax is suitable for screening patients with sperm concentrations below 5 million/mL. Volume-L combined with Emax-L offers a more accurate method for predicting semen parameter improvement after macroscopic subinguinal varicocelectomy. Our findings suggest that SWE can be used for men with varicocele to assess testicular parenchyma damage and predict semen improvement after varicocelectomy.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-8/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-8/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of Shengjing Hospital of China Medical

University (Reg. No. 2018PS104J). Written informed consent was provided by all participants.

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