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Investigating discordance between embryologists and histopathologists: analysis of multiple factors in mTESE sperm retrieval outcomes

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Abstract

The objective of the study is to primarily highlight the consistency between the embryologist and the histopathologist in microdissection testicular sperm extraction and to explore the factors affecting sperm retrieval. The research included 91 patients, aged 20 to 47, who visited our Reproductive Technology center from July 2020 to June 2023. Patient data were collected retrospectively, including demographics, physical exams, lab tests, radiological assessments, genetic analyses, medical histories and histopathological results. Using the Johnsen scoring system for evaluation, the histopathologist identified mature spermatozoa in the specimen in some patients (Johnsen score 8–10); however, the embryologist only declared successful sperm retrieval in 66.6% of them. Overall sperm retrieval rates were lower than expected at 40%. Significant factors influencing sperm retrieval rates included Follicle Stimulating Hormone ($p = 0.001$), Luteinizing Hormone ($p = 0.007$), testicular volume ($p < 0.001$), histopathology ($p < 0.001$), and alcohol consumption ($p = 0.007$). A logistic regression model was used to identify the independent predictors of successful sperm retrieval. FSH ($p = 0.038$), testicular volume ($p < 0.001$), histopathology ($p < 0.001$), and alcohol consumption ($p = 0.013$) emerged as significant predictive factors for the outcome of sperm retrieval. As a result, in addition to patient-related factors, the consistency between the pathologist and embryologist also affects sperm retrieval rates.

Keywords

Azoospermia; mTESE; Histopathology; Embriyology; Sperm retrieval

Investigando la discordancia entre embriólogos e histopatólogos: análisis de múltiples factores en los resultados de recuperación de esperma mediante mTESE

Resumen

El objetivo del estudio es destacar principalmente la consistencia entre el embriólogo y el histopatólogo en la extracción de espermatozoides testiculares por microdisección y explorar los factores que afectan la recuperación de espermatozoides. La investigación incluyó a 91 pacientes, de 20 a 47 años, que visitaron nuestro centro de Tecnología Reproductiva desde julio de 2020 hasta junio de 2023. Se recopilaron datos retrospectivamente, incluyendo datos demográficos, exámenes físicos, pruebas de laboratorio, evaluaciones radiológicas, análisis genéticos, historias médicas y resultados histopatológicos. Utilizando el sistema de puntuación de Johnsen para la evaluación, el histopatólogo identificó espermatozoides maduros en la muestra en algunos pacientes (puntuación de Johnsen 8–10); sin embargo, el embriólogo solo declaró recuperación exitosa de espermatozoides en el 66.6% de ellos. En general, las tasas de recuperación de espermatozoides fueron más bajas de lo esperado, con un 40%. Los factores significativos que afectaron las tasas de recuperación de espermatozoides incluyeron Hormona Folículo Estimulante ($p = 0.001$), Hormona Luteinizante ($p = 0.007$), volumen testicular ($p < 0.001$), histopatología ($p < 0.001$) y consumo de alcohol ($p = 0.007$). Se utilizó un modelo de regresión logística para identificar los predictores independientes de la recuperación exitosa de espermatozoides. FSH ($p = 0.038$), volumen testicular ($p < 0.001$), histopatología ($p < 0.001$) y consumo de alcohol ($p = 0.013$) surgieron como factores predictivos significativos para el resultado de la recuperación de espermatozoides. Por lo tanto, además de los factores relacionados con el paciente, la consistencia entre el patólogo y el embriólogo también afecta las tasas de recuperación de espermatozoides.

Palabras Clave

Azoospermia; mTESE; Histopatología; Embriología; Recuperación espermática

1. Introduction

Azoospermia is the complete absence of sperm in the semen and affects about 1% of men [1]. It is categorized as obstructive azoospermia (OA), caused by blockages in the reproductive system, and non-obstructive azoospermia (NOA), resulting from sperm production issues. OA is less common, with an estimated incidence of 20–40% [2].

Testicular sperm extraction (TESE) is a surgical method used to retrieve sperm from the testicles in patients with NOA. There are two types of TESE: conventional (cTESE) and microscopically (mTESE). mTESE allows better evaluation of dilated, opaque and larger seminiferous tubules, which are thought to be more likely to contain sperm. This is done using a surgical optical microscope at 20–25 times magnification. However, there is an ongoing debate about whether mTESE has superior sperm retrieval rates (SRR) compared to cTESE, with various findings reported in the literature [3]. Nonetheless, there is a tendency among andrologists to prefer mTESE if possible when choosing between the two procedures.

The SRR of mTESE is approximately 50% [4]. Several factors, including age, testicular volume, hormone levels (Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH)), and testicular histopathology, can influence the success of mTESE [1]. Additionally, levels of Inhibin B [5] and Anti-Mullerian Hormone [6] may serve as predictive factors. Notably, the experience and proficiency of the medical team are crucial in achieving successful outcomes, from sperm retrieval to the overall success of assisted reproductive techniques [7].

Although research has been ongoing, there is currently no definitive marker for successful sperm retrieval (SR) in TESE. Failing SR in TESE not only has financial implications but can also have emotional consequences [8]. The stress caused by multiple invasive procedures and the financial burden can be significant. Additionally, there is a potential risk of developing hypogonadism after failed bilateral micro-TESE [9].

Our study aims to identify factors that affect sperm retrieval rates (SRR) in micro-TESE and evaluate the impact of laboratory team factors on the procedure. In our cohort, some patients had mature spermatozoa found by the pathologist in samples taken during the same session, yet the SR was unsuccessful according to the embryologist. There is a lack of literature exploring the connection between team experience, consistency, and SRR, which is what motivates our study. Ultimately, we aim to establish a comprehensive decision-making process that takes success-influencing factors into account before recommending invasive procedures.

2. Materials and method

We conducted a retrospective analysis of 91 azoospermic patients who underwent mTESE at our Assisted Reproductive Technology Center between July 2020 and June 2023. Eight of these patients had previously been diagnosed with OA and had undergone unsuccessful microsurgical epididymal sperm aspiration (MESA). The remaining 83 were diagnosed with NOA, confirmed through physical examination, medical history, hormonal evaluation, genetic testing and semen analyses.

We gathered information on the patient's age, smoking, and alcohol consumption, history of previous inguinoscrotal surgery, as well as their physical examination and clinical findings from their medical records. Testicular volumes and varicocele status were determined using a Prader orchidometer or scrotal doppler ultrasound.

The hormonal analysis involved evaluating levels of FSH, LH and total testosterone in peripheral venous blood taken at 10 AM after an 8-hour fast. Normal values for FSH, LH and total testosterone values were considered as 1.5–12.4 mIU/mL, 1.7–8.6 mIU/mL and 2.8–8 ng/mL, respectively. Genetic analysis included karyotype analysis and Y chromosome microdeletion analysis conducted on peripheral venous blood samples.

Ninety-one patients underwent mTESE with spinal anesthesia. The procedure involved making a median scrotal incision to expose the testicle, followed by incisions in various tissue layers. A specific area marked by Schlegel was used as a guide for incising the tunica albuginea [10]. Microdissection of the seminiferous tubules was conducted using a surgical microscope, with samples being taken from the tubules that appeared abnormal. These samples were immediately examined by the embryologist, who provided feedback on whether to continue the procedure and operate on the other testicle. Patients were categorized based on the presence (SR+) or absence (SR−) of spermatozoa. Biopsy samples from each treated testicle were taken randomly and underwent histopathological examination.

The histopathological assessment involved using the Johnsen Score (JS) to evaluate the status of spermatogenesis [11]. A score between 1 and 10 was assigned based on the spermatogenesis status (Table 1), with patients having a score of 8 or higher classified as Group I, indicating the specimen contains mature spermatozoa. Scores ranging from 3 to 7 were categorized as Group II, representing different stages of maturation arrest, while scores of 1 (Tubular Sclerosis) and 2 (Sertoli Cell Only) were classified as Group III, indicating no histopathological evidence of spermatogenesis. This categorization was established to investigate the correlation between successful sperm retrieval and the histopathological findings of spermatogenesis.

3. Statistical analysis

The statistical analysis was conducted using SPSS 24 statistical software (IBM, New York,USA). The results were reported as median (min–max). Pearson χ^2 test and Fisher's exact test were used to compare categorical variables, while the Mann-Whitney U test was used to analyze differences between quantitative data. Logistic regression analysis was performed to investigate parameters associated with SR. All p-values were two-sided, and statistical significance was considered at $p < 0.05$.

4. Results

Sperm were found in 36 of 91 patients, resulting in a 40% SRR. The median age for the groups with and without sperm retrieval was 33.5 (range 26–46) and 33 (range 20–47) respectively ($p = 0.118$). In the group with sperm retrieval, 18 out of 36 patients were smokers, while the group without sperm retrieval had 19

TABLE 1. Johnsen score.

Score	Level of spermatogenesis
10	Full spermatogenesis
9	Slightly impaired spermatogenesis
8	Less than five spermatozoa per tubule
7	No late spermatids; many early spermatids
6	Few early spermatids; arrest of spermatogenesis at the spermatid stage
5	Many spermatocytes
4	Few spermatocytes; arrest of spermatogenesis at the primary spermatocyte stage
3	Spermatogonia only
2	No germ cells; Sertoli cells only
1	No seminiferous epithelial cells; tubular sclerosis

out of 55 smokers ($p = 0.191$). 56.52% of the group with sperm retrieval consumed alcohol, while only 12.24% of the group without sperm retrieval did so ($p = 0.007$). The prevalence of varicocele was 38.46% in the group with sperm retrieval and 48.64% in the group without sperm retrieval ($p = 0.650$). The median FSH values were 9 in the group with sperm retrieval and 19 in the group without sperm retrieval ($p = 0.001$). The median LH values were 6.5 in the group with sperm retrieval and 10.1 in the group without sperm retrieval ($p = 0.007$). There was no significant difference in total testosterone levels ($p = 0.289$). The median testicular volume was 15.2 in the group with sperm retrieval and 7.5 in the group without sperm retrieval ($p < 0.001$). There was no significant correlation with surgical history ($p = 0.489$), karyotype analysis ($p = 0.603$) or Y chromosome microdeletion ($p = 0.962$). Johnsen score categorization SRR: 66.66% in Group I, 8.3% in Group II and 9.6% in Group III ($p < 0.001$). Table 2 presents the demographic, clinical, laboratory assessment, genetic analysis, and histopathological findings of the patients.

In the Receiver Operating Characteristic (ROC) curve analysis for testicular volume, an Area Under the Curve (AUC) of 0.838 was observed ($p < 0.001$). A cut-off value of 10.05 mL was identified as the most effective in predicting SRR. The results of the ROC curve analysis are visually presented and comprehensively summarized in Fig. 1 and Table 3.

When applying logistic regression analysis to all variables, age ($p = 0.011$), alcohol consumption ($p = 0.013$), FSH ($p = 0.038$), and histopathology ($p < 0.001$) were identified as independent predictive factors for successful SR, as outlined in Table 4.

5. Discussion

In our study, we looked into the factors that can impact SRR in mTESE. We used mTESE as the SR method for all patients. In our study, SRR was found to be 40%. However, with NOA a meta-analysis that included twenty-four studies reported a mTESE SRR rate of 45.1% [12]. It's important to recognize that SRR is affected by various factors. Among these factors, testicular histopathology appears to be potentially the most crucial. It's important to note that the embryologist considers factors such as sperm morphology and motility to determine the success of sperm retrieval, which differs from the approach of the histopathologist. Some studies suggest that histopathological evaluation with biopsy before TESE is a crucial predictor of SRR [13, 14]. In our clinical approach, we refrain from performing this procedure due to its inherent invasiveness, potential complications, and the heterogeneous nature of seminiferous tubules. Successful SR can be achieved with mTESE in patients histopathologically diagnosed with Sertoli Cell Only Syndrome, indicating that patients should not be strictly guided by biopsy results [15]. Consequently, we obtained the specimen for histopathological examination simultaneously with mTESE.

In their study, Yücel *et al*. [16] categorized the histopathology in salvage mTESE patients as follows: hyalinization of tubules (1), sertoli cell only (2), maturation arrest (3–7), hypospermatogenesis (8–9) and normal spermatogenesis (10). They reported SRR of 25%, 36%, 38%, 60% and 100%, respectively [16]. Cito *et al*. [17], who performed cTESE as sperm retrieval procedure, used the same categorizing in their study and found an SRR of 88.2% in normal spermatogenesis, 48.27% in hypospermatogenesis and 24.1% in maturation arrest group. No SR was observed in any patient in the Sertoli Cell Only group [17]. In contrast to these studies, we divided the histopathology into three groups. If the aim is to establish a predictive value for SRR, our method shows greater accuracy in yielding results. We believe that the presence of spermatozoa in histopathology should increase the likelihood of the embryologist finding usable sperm for ICSI. Additionally, unlike other studies, we obtained histopathology specimens during mTESE. Our outcomes provide a comprehensive picture due to the larger amount of specimens collected and the evaluation of different regions of the testicle.

While our Group I showed a significantly higher SRR, a comparison with other studies revealed that our patients with JS 8–10 had rates below those reported in the literature. This difference might stem from our hospital's ART center being recently established. Notably, our andrologist and histopathologist team brings substantial ART center experience from other hospitals. However, our embryologists, comparatively less experienced, have not been in ART centers for an extended duration.

The role of gonadotropins, especially FSH, in sperm produc-

TABLE 2. Demographic, clinical, laboratory assessment, genetic analysis, and histopathological findings of the patients.

	Sperm Retrieval+ N = 36	Sperm Retrieval− N = 55	*p* value
Age median (IQR)	33.5 (30.0–40.7)	33.0 (28.0–36.0)	0.118
Smoking (Yes/No)	18/18	19/36	0.191
Alcohol Consumption (Yes/No)	13/23	6/49	0.007
Varicocele status (Yes/No)	10/26	18/37	0.650
FSH median (IQR) (mIU/mL)	9.0 (4.5–12.9)	19.0 (8.5–29.0)	0.001
LH median (IQR) (mIU/mL)	6.5 (5.0–10.1)	10.1 (7.9–15.0)	0.007
Total Testosterone median (IQR) (ng/mL)	3.7 (2.8–4.6)	3.0 (2.0–5.0)	0.289
Testicular volume median (IQR) (mL)	15.2 (10.6–18.9)	7.5 (3.4–10.0)	<0.001
Operation History			
No operation	23	39	0.489
TESE	2	1	
MESA	4	4	
Varicocelectomy	3	6	
Orchiopexy	1	4	
Torsion	1	0	
Orchiectomy	2	1	
Karyotype analysis			
46, XY	35	47	0.603
47, XXY	1	5	
46, XY/47, XXY (mosaic)	0	1	
46, XY (INV 9 P11Q13)	0	1	
45 X (28), 46 XY (22)	0	1	
Y Chromosome microdeletion			
No	34	47	0.962
AZFc	2	3	
Partial AZFc	0	1	
AZFb + c + d	0	2	
Partial AZFb + c	0	1	
Partial AZFa	0	1	
Histopathology			
Group I	32	16	<0.001
Group II	1	11	
Group III	3	28	

Pearson χ^2 test were used for smoking, alcohol consumption, varicocele status and histopathology.
Mann Whitney U test were used for age, FSH, LH, total testosterone and testicular volume.
Fisher's exact test were used for operation history, karyotype analysis and Y Chromosome microdeletion.
IQR: interquartile ranges; FSH: follicle stimulating hormone; LH: luteinizing hormone; TESE: testicular sperm extraction; MESA: microsurgical epididymal sperm aspiration; AZF: azoospermia factor.

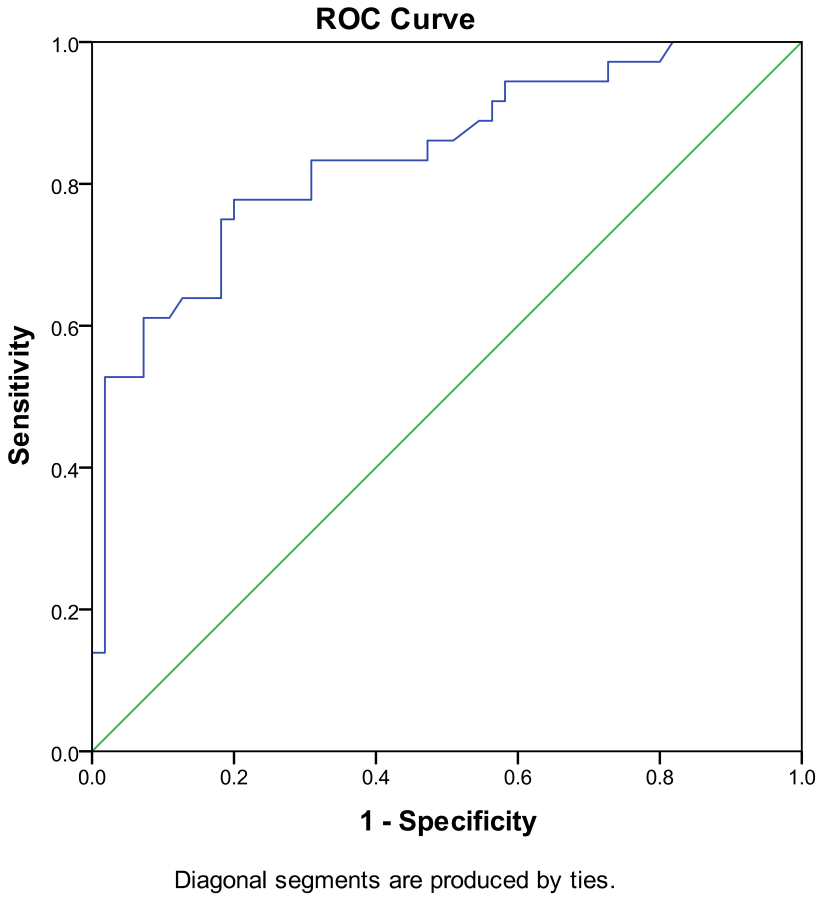

FIGURE 1. ROC curve analysis for testicular volume. ROC: Receiver Operating Characteristic.

TABLE 3. ROC Curve analysis and Youden index results for testicular volume.

	AUC (95% CI)	Cut off	*p* value	Sensitivity %	Specifity %
Testicular volume	0.838 (0.752–0.924)	10.05	<0.001	77.8	78.2

AUC: Area Under the Curve; CI: Confidence Interval.

TABLE 4. Logistic regression analysis of variables.

	OR	95% CI Lower limit–Upper limit	*p* value
Age	0.89	0.819–0.974	0.011
Smoking	0.92	0.340–2.536	0.885
Alcohol consumption	0.20	0.060–0.716	0.013
FSH	1.06	1.003–1.130	0.038
LH	0.98	0.885–1.091	0.740
Total testosterone	0.94	0.826–1.076	0.384
Testicular volume	0.76	0.688–0.860	<0.001
Operation history	1.19	0.875–1.620	0.226
Chromosome analysis	1.96	0.305–12.631	0.477
Y Chromosome microdeletion	3.13	0.594–16.504	0.179
Varicocele status	1.58	0.585–4.308	0.365
Histopathology	5.39	2.527–11.503	<0.001

FSH: follicle stimulating hormone; LH: luteinizing hormone; OR: Odds Ratio; CI: Confidence Interval.

tion is crucial. In the study conducted by Banerjee *et al.* [18], patients who underwent TESE were categorized into three groups based on their FSH levels: Group A (<10 mIU/mL), Group B (10–20 mIU/mL), and Group C (>20 mIU/mL). They found that Group A had a sperm SRR of 84%, Group B had 75%, and Group C had 15% [18]. Deng *et al.* [19] also showed that lower FSH levels were associated with successful sperm retrieval. Our study further confirmed that higher FSH levels negatively impact SRR. Therefore, FSH should be considered a predictive factor for SRR after histopathology.

Although we found that LH was a significant predictor of SRR, its predictive value was deemed insignificant in logistic regression analysis, which is consistent with the findings of Xu *et al*. [20]. They demonstrated that LH levels were not significantly different between successful and unsuccessful SR groups. Likewise, Deng *et al*. [19] found no significant effect of LH on SRR.

In a meta-analysis of 5 studies involving 1764 cases, it was concluded that testicular volume had a limited impact on SRR [21]. However, it is worth noting that the varied distribution of testicle volumes in the studies analyzed ranged from 2 mL to 16 mL. Our research, along with that of Kizilkan *et al*. [22], showed an increasing SRR with larger testicular volumes, with a suggested cut-off at 11 mL. Another recent meta-analysis proposed a cut-off of 12 mL, predicting successful SR with 86% accuracy [3]. Due to the varied results on testicular volumes, we suggest conducting future multicenter, prospective studies involving diverse patient populations to further explore this relationship.

A study conducted in China showed that there was a notable improvement in sperm parameters and unassisted pregnancy rates after microscopic varicocelectomy in patients with NOA [23]. Varicocelectomy was advised for all patients diagnosed with varicocele before undergoing mTESE. However, only 9 out of 28 patients (32.1%) chose to undergo the operation due to factors related to their partners and personal preferences. In an observational study involving 327 patients with NOA and a history of orchidopexy, SRR of 52.6% was achieved with mTESE. Additionally, fertilization, pregnancy, and live birth rates of 55.2% $\pm$ 20.5%, 53.5% and 44.8%, respectively, were observed. The success rate was significantly higher in individuals who underwent orchidopexy before the age of 9.5 years and in those with a testicular volume of $\geq$13.75 mL [24]. In a recent retrospective study, SRR were examined in NOA patients who underwent surgery for bilateral cryptorchidism. The study initially found a significant relationship between preoperative testicular localizations and SR rates. However, further analysis determined that testicular localization did not have a significant effect on SRR [25]. There was no significant relationship found between a history of previous inguinoscrotal surgery and SRR. Further studies with larger patient cohorts for each surgical method are recommended.

In a study investigating SRR of patients with Klinefelter syndrome, a 71% SRR was achieved in patients under 20 years of age, while a 52% SRR was achieved in patients over 20 years of age [26]. Another study, which involved 67 patients with Klinefelter syndrome, reported an SRR of 47.8% [27]. Interestingly, except for a few special cases, the SRR rates for patients with abnormalities detected in karyotype analysis seem to be similar to those of patients with NOA in general. The fact that only 1 out of 7 47, XXY patients had successful sperm retrieval in our study serves as another indicator of team incompatibility.

While AZFc microdeletion is the most common, isolated AZFa and AZFb microdeletions are exceedingly rare. As a result, there is limited SRR data on these rare microdeletions. In a newly published meta-analysis, it was found that patients with AZFc microdeletions exhibited a higher rate of SRR compared to those with other microdeletions; however, it was emphasized that this difference was not statistically significant [28]. In a study by Abur *et al*. [29], a 53.3% SRR was reported in NOA patients with AZFc microdeletion. In our study, successful SR was achieved in 40% of the patients with AZFc microdeletions, whereas it was not achieved in any of the patients with other types of microdeletions.

Contrary to the widely believed negative impact of alcohol and smoking on semen analysis [30], our study found no significant association between smoking and SRR. Interestingly, alcohol consumption showed a positive influence on SRR, indicating significant predictive value in logistic regression analysis. These findings need to be validated through more extensive studies. If future studies are planned, they should include details on the quantity and duration of alcohol consumption. It's important to note that these results may not accurately represent the entire population of infertile males.

While our study provides valuable insights, it is important to acknowledge some limitations. These include small sample size, retrospective nature of the study, limited evaluation of karyotype anomalies and Y chromosome microdeletions, and the absence of exploration into reproductive conditions after mTESE.

6. Conclusions

Our findings revealed that testicular histopathology, FSH levels, alcohol consumption, and testicular volume are predictive factors for sperm retrieval rates (SRR). By reclassifying histopathology in a non-traditional manner, we were able to achieve a more accurate interpretation of the histological results. However, it is crucial to emphasize that further validation of our results is necessary through studies involving a larger cohort of patients. Additionally, we suggest conducting comparative research to evaluate the impact of embryologist experience on SRR outcomes.

AVAILABILITY OF DATA AND MATERIALS

The data cannot be shared due to full compliance with the data protection law of the local administration.

AUTHOR CONTRIBUTIONS

MS—designed the research study, performed data analysis and wrote the manuscript. OC—performed data analysis and wrote the manuscript. ETK—performed data analysis and wrote the manuscript. YCF—performed data analysis, wrote the manuscript. HLC—developed the project and edited

the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the local ethics committee at University of Health Sciences Basaksehir Cam and Sakura City Hospital (No: KAEK/08.11.2023.558). All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and this study was designed according to the STROCSS 2021 criteria. The patients provided informed consent and agreed to publication of the details of this research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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