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ORIGINAL ARTICLE

Can systemic inflammatory markers predict sperm retrieval with the micro-TESE procedure in patients with non-obstructive azoospermia? A tertiary IVF center experience

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ABSTRACT

Objective: We aim to investigate the relationship between the pro-inflammatory markers and sperm retrieval (SR) in microdissection testicular sperm extraction (micro-TESE) procedure in patients with non-obstructive azoospermia (NOA).

Material and Methods: This retrospective study was conducted with 318 patients who applied to our in vitro fertilization Unit between April 2017 and December 2020 and underwent micro-TESE for NOA. Patients with (Group 1) and without (Group 2) sperm retrieved were compared in terms of age, infertility duration, body mass index (BMI), hormone profile, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-eosinophil ratio (MER), platelet-to-lymphocyte ratio (PLR), and a new marker of eosinophil-to-lymphocyte ratio (ELR).

Results: SR from the micro-TESE procedure was achieved in 183 (57.5%) of 318 patients. Testicular tissue biopsies were performed simultaneously in all cases. There was no statistically significant difference between the groups concerning BMI. When the groups were compared regarding the pro-inflammatory markers, while the NLR, MER, and PLR were found to be statistically higher in Group 2 cases; ELR was similar among groups.

Conclusion: The MER, NLR, and PLR were determined to be associated with negative micro-TESE results. Particularly PLR seems to have a poor prognostic value in these patients. A prognostic value of the ELR which was a new biomarker was not determined in SR from the TESE procedure.

Keywords: *In vitro* fertilization, inflammatory markers, non-obstructive azoospermia, sperm retrieval, testicular sperm extraction.

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INTRODUCTION

Patients with non-obstructive azoospermia (NOA) account for approximately 60% of azoospermic cases.[1] NOA manifesting itself with testicular failure is encountered as the most severe form of male infertility. Many disorders such as cryptorchidism, hypogonadotropic hypogonadism, chromosomal and genetic anomalies, undescended testicles, varicocele, mumps orchitis, testicular damage, history of chemotherapy, and radiotherapy are among the causes of NOA.[2–6]

Since the normal spermatogenesis is disrupted in males with testicular azoospermia, sperm retrieval (SR) is only possible with surgical intervention. The microdissection testicular sperm extraction (micro-TESE) procedure is an ideal surgical technique in which the seminiferous tubules are directly examined under the microscope in NOA cases and has been emerged as a gold standard in the way of becoming a father for these cases.[7]

No definitive clinical test is available to show whether spermatozoa are present in the testicles of the patients with NOA or not before the TESE procedure. On the other hand, some criteria which are considered to affect the SR rate are available. The most important ones of these criteria are as follows: The result of the previous testicular biopsy, the serum level of follicle-stimulating hormone (FSH), and testicular volume.[8] In recent years, studies related to the role of pro-inflammatory markers showing systemic inflammation in many inflammatory diseases, cancer is in the first place such as monocyte-to-eosinophil ratio (MER), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were reported.[9–11] Based on the knowledge of inflammatory processes causing an increase in free oxygen radicals and disturbing sperm functions, also the relationship between sperm parameters and inflammatory markers in infertile males has become the subject of research.[12]

We aim to investigate the relationship between the pro-inflammatory markers of MER, NLR, PLR, and a new marker of eosinophil-to-lymphocyte ratio (ELR) and SR in micro-TESE procedure in NOA cases.

MATERIAL AND METHODS

Procedure and Participants

The medical data of 441 patients presented to our in vitro fertilization Unit of a tertiary center hospital between the dates of April 2017 and December 2020 and diagnosed with NOA were retrospectively investigated. Cases among 18–55-year-old age who would undergo the micro-TESE procedure for the 1st time were included in the study. Exclusion criteria were as follows: Having chronic inflammatory disease, morbid obesity, hematological disorders, malignancies, patients receiving anticoagulant therapy, Y-chromosome microdeletions, Klinefelter syndrome, the presence of varicocele, the presence of active genital infection, and history of genital surgery. One hundred and twenty-three patients who met exclusion criteria were excluded from the study and the study was continued with 318 patients.

Ethical approval was obtained from the University Hospital Ethics Committee (decision number 189, dated 09/12/2020). All procedures in our study were carried out in accordance with the 1964 Declaration of Helsinki and subsequent amendments.

Demographic data, medical, and andrological data were recorded for each patient. While making the diagnosis of azoospermia, the parameters were confirmed with at least two analyses of semen samples (collected at 2 weeks intervals) obtained by masturbation from patients after 3–5 days of sexual abstinence, processed and evaluated according to the World Health Organization (2010) guidelines were used.[13] Medical history, physical examination, hormonal analysis, chromosomal, and genetic analysis parameters were used to distinguish NOA from obstructive azoospermia. However, the final diagnosis was made based on the results of testicular biopsies performed during the TESE procedure.[14] The histopathological results were investigated in five groups as follows: (i) Hypospermatogenesis, (ii) maturation arrest, (iii) Sertoli-cell-only (SCO), (iv) mixed atrophy, and (v) combined pattern. European association of urology guidelines recommends performing simultaneous testicular biopsy with the micro-TESE procedure to determine the cause of NOA and to define the histopathology.[15] In our clinic, we routinely perform a simultaneous testicular biopsy with the micro-TESE procedure in patients with NOA.

The patients were investigated in two groups regarding SR in the micro-TESE procedures. The Group with SR was named as Group 1 (n:183) and the group without SR (WSR) was named as Group 2 (n:135). Both groups were compared regarding age, duration of infertility, body mass index (BMI), hormone profile, the NLR, MER, PLR, ELR, and other hematological parameters.

Sample Collection, Laboratory, and Genetic Analysis

Hormone profile was evaluated with measurements of Testosterone (T), FSH, Luteinizing Hormone (LH), and Prolactin levels in the venous blood sample taken between 08:00 and 10:00 a.m. Serum samples were analyzed using Immulite 2000 reproductive hormone assays.

Peripheral blood taken from all patients was incubated in a complete lymphocyte culture medium (in Roswell Park Memorial Institute-1640 with 2.5% phytohemagglutinin and 2% l-glutamine and 1% penstrept) in an incubator at 37°C for 72 h. Chromosome preparations were stained using GTG-banding. Karyotype analysis was performed using a protocol with a 550–700 bands resolution for each patient.

The pre-operative complete blood counts asked for surgical preparation before the TESE procedure was evaluated. The complete blood counts were analyzed by an automated hematology analyzer (CELL-DYN 3700, Abbott Diagnostics, Abbott Park, IL). NLR, MER, PLR, and ELR were calculated.

Micro-TESE Technique

Written informed consent was obtained from all patients before the TESE procedure. Since the micro-TESE procedure would be coupled with ICSI, it was performed on the day before oocyte retrieval. Since sperm may rarely spill over into the ejaculates of such patients, the presence of azoospermia was confirmed with a centrifuged semen specimen obtained immediately before the procedure. Procedures were performed under intravenous anesthesia on an outpatient basis. A midline vertical anterior scrotal incision, 4 cm in length, was made and the tunica albuginea of the testis

was exposed and the testis was reached. At first, the testis with a larger volume was preferred. After delivery of the testis, the tunica albuginea was exposed transversely under 6–8× magnification with the help of an operation microscope by defining avascular areas in the antimesenteric region. Then, the testicular parenchyma was investigated under 15–25× magnification. Opaque, white tubules in the testicular parenchyma were selectively removed in small pieces (5–10 mg) under the microscope. The samples were placed in a Petri dish filled with Bouin's solution. Then they were evaluated by the embryologist in the same session under 200× magnification with the help of a microscope. When suitable spermatozoa were found for ICSI, the procedure was terminated. In cases where the spermatozoa were not found, the same procedures were carried out on the contralateral testis. The samples were taken in cases in which no sperm were found after mechanical processing was subjected to enzymatic digestion with collagenase Type IV (1000 IU ml–1) for approximately 2–4 h. Final approval regarding SR was determined after this procedure. All micro-TESE procedures were performed by the same urologist. Testicular tissue biopsies were performed simultaneously in all cases during the micro-TESE procedure.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 17 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as number (%), mean±standard deviation, as appropriate. Kolmogorov–Smirnov test was used to test the distribution of continuous data. Two independent means were compared with the Student's t-test or the Mann–Whitney U-test.

The ability of the parameters to predict the presence of spermatozoa in the TESE procedure was investigated by the receiver operating curve (ROC) analysis, and the threshold values were calculated using the Youden Index Method. Specific thresholds were reviewed individually with the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. The independent effect of variables affecting SR by the TESE procedure was evaluated with multivariate logistic regression analysis.

The relationship between testicular histopathology and systemic inflammatory markers was investigated by using Spearman's rho correlation test. The study was performed at a confidence level of 95%. Statistical significance was set at p≤0.05.

RESULTS

Clinical features, hormonal profiles, and hematological parameters of patients are shown in Table 1. SR from the micro-TESE procedure was achieved in 183 (57.5%) of 318 patients diagnosed with NOA and planned to undergo ICSI. While sperm was found at first examination in 154 patients (84.2%), it was observed that sperm was obtained after enzymatic digestion in 29 patients (15.8%). Testicular tissue biopsies were performed in all cases. The mean age of the patients was 35.71±6.80 years in Group 1 cases and 34.19±6.27 years in Group 2 cases. No statistical difference was determined between the two groups. When the cases were compared regarding the duration of infertility, this period was average of 4.62±1.76 years for Group 1 and 4.71±1.67 years for Group 2. No statistical difference was determined between the two groups. In terms of hormonal parameters, the serum FSH, LH, and E2 levels were found to be higher in Group 2 cases (respectively, p<0.001, p<0.001, and p<0.036). There was no statistically significant difference between the groups concerning BMI (p=0.102) (Table 1).

Table 1: The clinical characteristics, hormone, and hematologic parameters of micro-TESE patients in Groups 1 and 2

Characteristic	Group 1 (SR+) n: 183 Mean±SD	Group 2 (SR–) n: 135 Mean±SD	p
Age (years)	35.71±6.80	34.19±6.27	0.065
BMI (kg/m^2)	25.37±3.14	26.19±3.64	0.102
Duration of infertility (years)	4.62±1.76	4.71±1 67	0.504
Testosterone (ng/dl)	4.20±1.63	3.69±1.68	**0.005***
FSH (mIU/mL)	13.54±11.25	20.88±15.11	**<0.001***
LH (mIU/mL)	7.62±5.80	10.29±7.35	**<0.001***
Estrodiol (pg/mL)	27.78±17 18	30.32±14.94	**0.036***
Prolactin (ng/mL)	11.19±6.22	12.14±7.66	0.243
WBC (×10^3 per μL)	7.37±1.71	7.86±1.66	**0.005***
Neutrophil (×10^3 per μL)	4.22±1.28	4.72±1.22	**<0.001***
Monocyte (×10^3 per μL)	0.50±0.16	0.58±0.16	**<0.001***
Lymphocyte (×10^3 per μL)	2.53±0.69	2.41±0.66	0.168
Eosinophil (×10^3 per μL)	0.25±0.15	0.21±0.12	**0.033***
Basophil (×10^3 per μL)	0.03±0.03	0.03±0.04	0.168
RBC(×10^3 per μL)	5.00±0.43	5.07±0.35	0.266
Hemoglobin (g/dL)	14.82±1.15	14.90±1.13	0.238
Hematocrit (%)	43.56±3.20	43 97±2.76	0.209
MCV	87.58±4.22	87.40±4.17	0.699
MCH	29.79±1.66	29.64±1.98	0.657
MCHC	33.35±1.21	33.40±1.82	0.227
Platelet (x10^3 per μL)	226.50±55.92	277.48±70.81	**<0.001***
NLR	1.79±0.77	2.06±0.73	**<0.001***
MER	2.66±1.96	3.30±2.15	**0.001***
ELR	0.098±0.064	0.090±0.063	0.217
PLR	92.09±23.95	123.52±44.53	**<0.001***

SD: standard deviation; SR: Sperm retrieval; BMI: Body mass index; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; NLR: Neutrophil-to-lymphocyte ratio; MER: Monocyte-to-eosinophil ratio; ELR: Eosinophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; *: Statistically significant difference.

Table 2: The histopathological results of the testis tissues examined after the micro-TESE operation and the SRR results

Histopathological findings	Group 1 (SR+) n: 183		Group 2 (SR–) n: 135		p	
	n	%	n	%	n	%
Hypospermatogenesis	40	80	10	20	50	100
Sertoli cell only	25	28.7	62	71.3	87	100
Maturation arrest	80	69.6	35	30.4	115	100
Mixed atrophy	27	60	18	40	45	100
Combined pathology	11	52.4	10	47.6	21	100

SRR: Sperm retrieval rate; p-value <0.001; SR: Sperm retrieval.

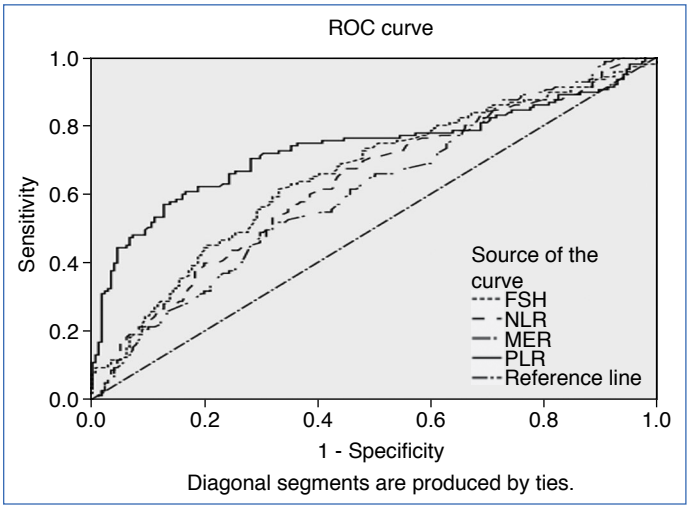

Figure 1: ROC analysis evaluating the prediction of SR by hematological parameters.

ROC: Receiver operating characteristic; FSH: Follicle-stimulating hormone; NLR: Neutrophil/lymphocyte ratio; MER: Monocyte/eosinophil ratio; PLR: Platelet/lymphocyte ratio.

Table 3: Best cutoff values in which FSH, NLR, MER, and PLR can predict sperm retrieval in micro-TESE, sensitivity, specificity, PPV, NPV, and accuracy percentages

Cut-off values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AR (%)	p
FSH ≥13	63.70	61.20	54.78	69.57	60.38	**<0.001**
NLR ≥1.7	66.67	55.19	52.33	69.18	60.06	**<0.001**
MER ≥2.56	51.85	67.26	54.26	65.61	61	**0.001**
PLR ≥101	70.37	70.49	63.76	76.33	70.44	**<0.001**

FSH: Follicle-stimulating hormone; NLR: Neutrophil-to-lymphocyte ratio; MER: Monocyte-to-eosinophil ratio; PLR: Platelet-to-lymphocyte ratio; PPV: Positive predictive value; NPV: Negative predictive value; AR: Accuracy ratio.

When hematological parameters were evaluated, a statistical difference was determined between the two groups regarding leukocyte, neutrophil, monocyte, eosinophil, platelet values. While the numbers of leukocyte, neutrophil, monocyte, and platelet were determined to be significantly higher in Group 2 cases (p=0.005, p<0.001, p<0.001, and p<0.001; respectively); the number of eosinophils was determined to be higher in Group 1 cases (p=0.033). When the groups were compared regarding pro-inflammatory markers, the NLR, MER, and PLR were found to be statistically significantly higher in Group 2 cases (p<0.001, p=0.001, and p<0.001; respectively). ELR which was considered as a new bio-marker by us was determined to be similar rates between the groups (p=0.217) (Table 1).

When we evaluated the groups regarding the histopathological findings (Table 2); while the most commonly determined histopathological finding in the group with SR was maturation arrest, the most commonly determined histopathological finding in the group WSR was SCO (p<0.001). The highest SR rate was present in NOA cases with hypospermatogenesis histopathology (80%). The relationship between testicular histopathologies and systemic inflammatory markers was investigated by using Spearman's rho correlation test. No relationship was determined between none of systemic inflammatory markers and histopathologies (NLR; r=–0.006, p=0.917, MER; r=–0.107, p=0.056, PLR; r=–0.092, p=0.103, and ELR; r=–0.029, p=0.608).

ROC analysis was performed to calculate the cutoff value for the determination of the value of statistically significant FSH and pro-inflammatory markers indicating the presence of sperm (Fig. 1). Sensitivity, specificity, PPV, NPV, and accuracy rate (AC) were calculated with the cutoff value obtained in the ROC analysis. ROC curve is shown in Figure 1. Sensitivity, specificity, PPV, NPV, and AC calculated according to the best threshold values of the FSH, NLR, MER, and PLR which could predict SR in the micro-TESE procedure are shown in Table 3. The best threshold value of the NLR which can predict SR in the TESE procedure is 1.70 (sensitivity: 66.67%, specificity: 55.19%, PPV: 52.33%, NPV: 69.18%, AC: 60.06%) (AUC: 0.63, 95% CI 0.568–0.692, p<0.001). The best threshold value of MER which can predict SR in the TESE procedure is 2.56 (sensitivity: 51.85%, specificity: 67.76%, PPV: 54.26%, NPV: 65.61%, AC: 61%) (AUC: 0.609, 95% CI 0.546–0.671, p=0.001). The best threshold value of PLR which can predict SR in the TESE procedure is 101 (sensitivity: 70.37%, specificity: 70.49%, PPV: 63.76%, NPV: 76.33%, AC:

Table 4: Factors affecting sperm retrieval by micro-TESE independently according to multivariate logistic regression analysis

Variables	OR	95 % CI	p
Age	0.0967	0.928–1.009	0.119
BMI	1.114	1.027–1.207	**0.009**
FSH ≥13	3.115	1.817–5.339	**<0.001**
NLR ≥1.7	1.780	1.032–3.069	**0.038**
MER ≥2.56	3.011	1.730–5.242	**<0.001**
PLR ≥101	5.778	3.111–10.083	**<0.001**

AOR: Adjusted odss ratio (multiple imputation model adjusted for age); BMI: Body mass index; FSH: Follicle-stimulating hormone ≥13; Neutrophil/lymphocyte ratio: NLR ≥1.7; MER: Monocyte/eosinophil ratio ≥2.56; PLR: Platelet/lymphocyte ratio ≥101.

70.44%) (AUC: 0.73, 95% CI 0.670–0.79, p<0.001). When the cutoff value of the FSH was considered to be 13, sensitivity, specificity, PPV, NPV, and AC of this test in the prediction of SR were found to be 63.70%, 61.20%, 54.78%, 69.57%, and 60.38%; respectively (AUC: 0.654, 95% CI 0.593–0.716, p<0.001). Independent effects of variables affecting SR with the TESE procedure were investigated by the Logistic regression analysis (Table 4). It was observed that BMI, the NLR ≥1.70, MER ≥2.56, PLR ≥101, and FSH ≥13 were independent variables in the prediction of SR and PLR was the most successful prognostic marker among these variables (OR: 5.778 95% CI 3.111–10.083; p<0.001).

DISCUSSION

Until today, a routine clinical test that could predict SR of NOA cases in the TESE procedure was not defined. In the studies performed until today, some parameters considered to influence the probability of retrieving spermatozoa in the TESE procedure were suggested. Since these predictors can be clinical (cryptorchidism, testicular volume, BMI, paternal age, and varicocele), laboratory (FSH, Inhibin B), genetic (Klinefelter syndrome and Y-chromosome microdeletions) parameters, also testicular histology is among the most commonly investigated predictors.[5,16] The presence of SCO has been reported to be a poor predictor of successful SR.[5] We determined the SR rate to be 57.5% for all patients in our study. We determined that hypospermatogenesis predicted SR in the TESE procedure with the highest rate and SCO indicated the worst prognosis on this subject.

In a study investigating the relationship between serum FSH levels and successful SR, a total of 1371 cases undergoing TESE procedures were investigated and lower levels of FSH were reported to be predictive for successful SR.[17] We determined that elevated serum FSH levels were an independent variable for successful SR in our study. Individually, serum FSH levels may not predict spermatogenesis correctly. Because men with a diagnosis of azoospermia and maturation arrest histology may have normal FSH levels and a normal testicular volume.[18] Therefore, FSH does not provide consistent and sufficient evidence for SR in the TESE procedure.

It has been shown previously that increased BMI negatively affected semen parameters in fertile men by causing higher seminal ROS, and sperm DNA fragmentation.[19] In the study of Karamazak et al.,[20] no statistically significant difference was found in SR rates between subgroups classified according to BMI. While BMI values of patients WSR were higher in our study, the difference between the groups was not found to be statistically significant. However, we considered BMI as an independent variable affecting the SR rate even with a lower value.

In recent years, the relationships between the aforementioned clinical and pathological predictors as well as laboratory predictors (pro-inflammatory markers) and semen parameters and SR in the TESE procedure were investigated in patients with NOA.[21,22] Thus, the role of systemic inflammatory markers in premature ovarian insufficiency patients (which corresponds to testicular failure patients in women) was investigated and it was reported to be a promising marker in the early diagnosis of premature ovarian insufficiency.[23] Having a role of inflammatory conditions in 15% of patients also in men became the starting point of these studies.[24] Since it is not easy to attribute inflammatory symptoms specifically to an organ in male infertility studies, the diagnosis is mainly based on semen abnormalities.[25] Increased levels of cytokines and emerging oxidative stress in conditions of inflammation impair sperm production and damage sperm DNA and cause apoptosis in sperm.[26,27]

In the pilot study performed by Yucel et al.,[21] the effect of asymptomatic systemic inflammation on the success of the TESE procedure in patients with NOA was investigated. The authors reported that NLR and PLR play a predictive role in the prediction of SR. We also determined NLR, MER and PLR to be associated with negative TESE results in our study. In the study performed by Yucel et al.,[21] not assessment of the correlation between the testicular histopathologies and systemic inflammatory markers can be considered as a limitation of the study. We investigated this correlation in our study and determined no relationship between the testicular histopathologies and systemic inflammatory markers (the NLR, MER, PLR, and ELR).

Aykan et al.[22] compared 57 infertile couples with abnormal semen parameters and 59 fertile men with normal semen parameters and evaluated the relationship of seminal parameters with the NLR and the PLR values. At the end of the study, no correlation was reported between these seminal parameters and the NLR or PLR values (p>0.05). A relatively small number of patients and inclusion of all patients with abnormal semen parameters might have led to the inability of biomarkers to reflect systemic inflammatory response.

In another study performed by Öztekin et al.,[28] the authors compared 80 patients with abnormal semen analysis and 80 patients with normal semen analysis regarding systemic inflammatory markers (the NLR, PLR, and RPR). At the end of the study, the authors concluded that the NLR, PLR, and RPR results could not be used as a predictive marker on abnormal sperm parameters in infertile men. Different from our study, also in this study, not only azoospermic patients were investigated and all-male infertile patients were included in the study.

Eosinophil-based ELR which was previously used in cancer researches was investigated for the 1st time in our study for TESE

success of patients with NOA. However, contrary to the NLR, MER, and PLR, ELR was not found to be associated with negative TESE results. The ELR was used for the 1st time to evaluate its impact on the overall survival of endometrial cancer patients in a study performed by Holub and Biete and defined as a poor prognostic indicator.[29]

Our study has some limitations. Reflection of a single-center experience, not the evaluation of cigarette smoking and retrospective design is the main limitation of our study. Our study also has strengths. Diagnosis of patients with NOA included in the study, clinical, genetic, hormonal assessments as well as histopathological results of the testicular biopsy specimens taken during the TESE procedure was set as the gold standard. As a matter of fact, in the study of Güler et al.,[30] it was revealed that testicular histology is a significant variable to predict successful SR in TESE. Our study was the second study in the literature investigating the ability of pro-inflammatory markers in predicting the presence of sperm in the TESE procedure of patients with NOA and the histopathological data could not be presented in the previous pilot study differently from our study.[20] Furthermore, the larger number of cases compared to other andrological diseases in which the predictive value of pro-inflammatory markers is investigated is another strength of our study.

CONCLUSION

The NLR, MER, and PLR were determined to be associated with negative micro-TESE results in infertile men with NOA. Particularly PLR seems to have a poor prognostic value in these patients. A prognostic value of ELR which was a new biomarker was not determined. Hematological markers are practical and cost-effective pro-inflammatory markers that can be easily calculated with routine complete blood count tests controlled before the TESE procedure. Routine use of these hematological markers for male infertility in the future may be beneficial in the early diagnosis of azoospermic patients. Since there are too few studies performed with NOA patients in the literature, a larger number of multicenter, prospective studies are required to be able to present the relationship between systemic inflammatory markers and the success of the TESE procedure more clearly.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 09.12.2020, number: 189).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BD, ET, EÖ, İŞ, EÇ; Design – BD, AA, GDRK; Supervision – NP, EÇ, EÖ; Resource – BD, AA, GDRK, ET; Materials – PK, BD, ET, EÖ, EÇ, İŞ; Data Collection and/or Processing – İŞ, NP, PK GDRK; Analysis and/or Interpretation – PK, EÖ, EÇ; Literature Search – BD, NP, EÖ, EÇ; Writing – BD, EÖ, EÇ, İŞ, ET, NP; Critical Reviews – BA, NP, EÇ, EÖ.

Conflict of Interest: The authors have no conflict of interest to declare.

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