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The investigation of retinoic acid on spermatogenetic cell types of rats

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Abstract

Background/Aim: Vitamin A is crucial for male fertility and the progression of the spermatogenetic process. Retinoic acid (RA), a metabolite of vitamin A, binds to three nuclear receptors, functioning similarly to a hormone by activating them. Our study aimed to investigate the effects of exogenous RA on spermatogenetic cell types, assessing them histochemically, immunohistochemically, and ultrastructurally.
Methods: We used three groups: a control group and experimental groups treated with 40 mg/kg RA and 80 mg/kg RA. Each group contained eight adult Sprague-Dawley rats. RA, dissolved in corn oil, was administered to the experimental groups via gavage for 3 weeks. After 3 weeks, testes from the sacrificed animals were evaluated using light and electron microscopy. The sections were stained histochemically with hematoxylin-eosin (H&E) and periodic acid Schiff (PAS). Seminiferous tubules in the rats were staged using PAS staining. The cellular localization of the RARα receptor in the seminiferous tubules was identified after immunohistochemical analysis.
Results: Immunoreactivity was qualitatively observed and graded from no staining to strong. In the immunohistochemical analysis, the experimental groups, particularly in stages VI, VII, VIII, and XIV, showed a significant difference in immunoreactivity compared to the control group. This difference was particularly evident in stage VI spermatogonia – the stage at which the first meiosis begins. A morphologically observed reduction in the seminiferous tubules, likely due to the loss of germ cells, was statistically significant in terms of the average diameter of the seminiferous tubules in the 80 mg/kg experimental group compared to both the control and the 40 mg/kg experimental group (P<0.001). Electron microscopic examination revealed an increase in intercellular distance, especially between basal compartment cells, in both experimental groups. Additionally, compared to the control group, both experimental groups showed an increase in the number of lipid-like granules on the membrane, particularly in the cytoplasm of spermatogonia and Sertoli cells.
Conclusion: Based on our observations, this study suggests that exogenous RA can impact the overall histology of the testis. Moreover, it may play a significant role in the meiosis process by influencing the internal dynamics of spermatogenetic cell types.

Keywords: 13-cis-retinoic acid, RARα, spermatogenesis, immunohistochemistry, electron microscopy

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Introduction

Retinoic acid (RA) serves as the biologically active derivative of vitamin A. It is transported into the nucleus by two receptor families, namely retinoic acid receptors (RARs) and retinoid X receptors (RXRs), both of which belong to the steroid/thyroid hormone receptor superfamily. Each of these receptor families is further divided into three isotypes: α, β, and γ, each with varying ligand binding affinities. RARs can bind to both all-trans and 9-cis retinoic acid, which are the two major naturally occurring derivatives of vitamin A. In contrast, RXRs exclusively bind to 9-cis RA. Ligands that specifically bind to RXRs are termed rexinoids [1].

In addition to its fundamental role in processes such as vision, growth, and cellular differentiation, RA is also essential for the proper functioning of reproductive organs. Numerous studies have demonstrated that both RA deficiency and excess have significant effects on the spermatogenic cells within the male reproductive organs, specifically the testes. However, the precise mechanisms underlying these effects have not yet been fully elucidated [2-4].

The presence of RARs in the development of male germ cells underscores the biological importance of RA in this process. In a study conducted on adult rats by Huang et al. [5] in 1994, it was observed that RARα was synthesized at varying rates not only in Sertoli cells but also in both spermatides and spermatocytes. The findings of this study suggest that RA may exert direct control over the differentiation of spermatogenic cells or do so indirectly through the actions of Sertoli cells. A deficiency or inactivity of RARα could potentially result in the selective deterioration of germ cells and trigger apoptosis [6]. Additionally, a connection has been proposed between RARs and germ cell apoptosis. In cases of RA deficiency or malfunction of the RARα receptor, male animals may become infertile due to testicle degeneration. Numerous studies have demonstrated that spermatogenesis can be reinstated by administering retinol, an RA precursor, to rats with vitamin A deficiency [7-10].

Our study aims to investigate the dose-dependent effects of RA on spermatogenic cells at histochemical, immunohistochemical, and electron microscopic levels. It is anticipated that our research will provide valuable insights into the role of RA in the mechanism of infertility.

Materials and methods

Experimental protocol

The animal experiments in this study were conducted in accordance with Decree No. 133 of the Local Ethics Committee of Istanbul University. Twenty-four adult male Sprague-Dawley rats, aged 6–8 weeks, were utilized for the study. Three groups, each comprising eight experimental animals, were formed in total. We employed 13-cis-RA (Isotretinoin, Roaccutane®, Hoffmann La Roche Ltd., Basel, Switzerland) in the form of 20 mg soft gelatin capsules for our experiment. To prepare the medication, 20 mg of 13-cis-RA was dissolved in a mixture of 4.5 ml of corn oil and 0.5 ml of ethanol. Each animal in the experimental groups received a daily dose of 1 ml of this medication via gavage feeding 5 days per week over a period of 3 weeks. The control group received normal saline treatment, whereas the experimental groups received 40 mg/kg and 80 mg/kg of 13-cis-RA.

Studies on the reproductive effects of 13-cis-RA have indicated that doses up to 30 mg/kg did not have significant effects on spermatogenesis [11]. However, a dose of 50 mg/kg resulted in testicular weight reduction and decreased spermatogenesis [12]. Hixson et al. [13] administered 40 mg/kg of 13-cis-RA to Sprague-Dawley rats and did not report any signs of toxicity.

At the conclusion of the experiment, the animals were anesthetized using 50 mg/kg of ketamine, and their abdominal cavities were opened. Subsequently, the testes were carefully extracted and immersed in appropriate solutions for examination under both light and electron microscopes.

Histochemical investigation

For light microscope analysis, the extracted testis tissues from the rats were initially placed in Bouin solution for 24 h. Subsequently, routine tissue processing methods were employed, and the tissues were embedded in paraffin. Sections were prepared and then evaluated using hematoxylin-eosin (H&E) and periodic acid Schiff (PAS) staining. The seminiferous tubules of the rats were staged using PAS staining.

RARα immunoreactivity

After dehydration, the 2 µm-thick sections were immersed in a 3% hydrogen methanol solution in the dark for 20 min to quench endogenous peroxidase activity. Subsequently, they were rinsed with phosphate-buffered saline, subjected to antigen retrieval, and then treated with a Kitin Blocking solution. After this blocking step, the sections were incubated with a 1/50-diluted primary antibody, RARα (Santa Cruz), overnight in a humidified container at +4°C.

On the following day, the sections were once again incubated, this time with a Biotinylated Goat Anti-Rabbit Secondary Antibody, in a humidified container for 20 min. Later, Streptavidin Peroxidase was applied for 20 min. Following these procedures, chromogen was applied to the sections in a dark container for 7–10 min. To assess background staining, the sections were counterstained with Ehrlich's Hematoxylin.

Transmission electron microscopy

For ultrastructural analysis, the testis tissues were initially immersed in a cacodylate-buffered solution containing 2.5% glutaraldehyde for fixation, and they were left in this solution for one day. Subsequently, routine tissue processing methods for transmission electron microscopy were carried out.

Statistical analysis

The data obtained in this study are presented as mean (standard deviation). To assess inter-group differences in seminiferous tubule diameters, a one-way analysis of variance (ANOVA) was employed. Subsequently, paired comparisons were analyzed using the Dunnett T3 test. The significance threshold was set at *P*-value <0.05, and the analyses were conducted using IBM SPSS Statistics 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Histochemical findings

All PAS-stained testis tissues from both the control and experimental groups were staged, and their spermatogenic serial cells were examined. In the control group, we observed spermatogonia and Sertoli cells in the basal compartments of seminiferous tubules, along with primary and secondary spermatocytes, as well as round, elongating, and elongated spermatids in the adluminal compartments (Figure 1a). The basal membrane structure of the seminiferous tubules and the acrosome structures of spermatids were positively stained with PAS (+).

Upon comparing the experimental groups with the control group, we observed a narrowing in the seminiferous tubule epithelium in both the 40 mg/kg-RA and 80 mg/kg-RA groups. Additionally, apart from the narrowing, which could be attributed to germ cell loss, the spermatogenic cells in most seminiferous tubules were found to be deformed (Figure 1b; Figure 1c).

RARα immunoreactivity

The results of immunohistochemical staining, conducted on both the control and experimental groups using the Rabbit Polyclonal Santa Cruz© brand RARα (c-20) antibody, were categorized based on seminiferous tubule sections. Each stage's spermatogenic serial cells and Sertoli cells were assessed individually, and you can find the corresponding findings in Table 1.

In stage VI, it was noted that both Sertoli cells and spermatogonia in the experimental groups exhibited higher RARα immunoreactivity in comparison to the control group. However, the spermatocytes and spermatids in the adluminal compartment exhibited lower immunoreactivity (Figure 2a, b, c).

In stages VII and VIII, both the control and experimental groups exhibited similar levels of RARα immunoreactivity in Sertoli cells, spermatogonia, and spermatocytes, with no significant differences. However, there was an increase in RARα immunoreactivity in spermatids and spermatozoa. Spermatozoa were only observed in stages VII and VIII, and initially, these cells showed no staining. Nevertheless, in stage VIII, a faint staining was observed.

Conversely, the experimental groups that received 40 mg/kg RA and 80 mg/kg RA displayed moderate and strong staining, respectively. In other words, RARα immunoreactivity in spermatozoa was significantly heightened in the RA-administered groups (Figure 3a, b).

In stage XIV, the RARα immunoreactivity in the Sertoli cells and spermatogonia within the basal compartment exhibited moderate staining in the control group. In contrast, both experimental groups displayed strong staining in these cell types. However, the degree of staining in spermatocytes and spermatids remained consistent between the control and experimental groups (Figure 4a, b).

Transmission electron microscopic evaluation

Upon detailed examination of thin sections, it became evident that the basal compartment contained both A and B-type spermatogonia along with Sertoli cells. In the adluminal compartments, primary and secondary spermatocytes were observed, while the region near the lumen contained round, elongating, and elongated spermatids, as well as spermatozoa.

Primary spermatocytes, characterized by type B spermatogonia with circular nuclei, were observed to have nuclei that appeared large and vesicle-like (Figure 5a).

As the largest cells within the seminiferous epithelium, primary spermatocytes were prominent in stages VII to XII (Figure 5b). In stage XIV, various phases of spermatocyte meiosis were observed (Figure 5c). The acrosome caps of round spermatids had expanded to cover approximately one-third of the spermatid head in stage VI and half of the head in stage VII. The Golgi bodies of round spermatids appeared normal (Figure 5d). In stage VIII, the circular nucleus of the spermatid was in contact with the plasma membrane (Figure 5e).

Spermatozoa were only visible in stages VII and VIII, characterized by their distinctive head, neck, and tail structures (Figure 5f). Examination of thin sections during these stages revealed the presence of tail sections, head structures, and residual material related to the spermatozoa within the lumen.

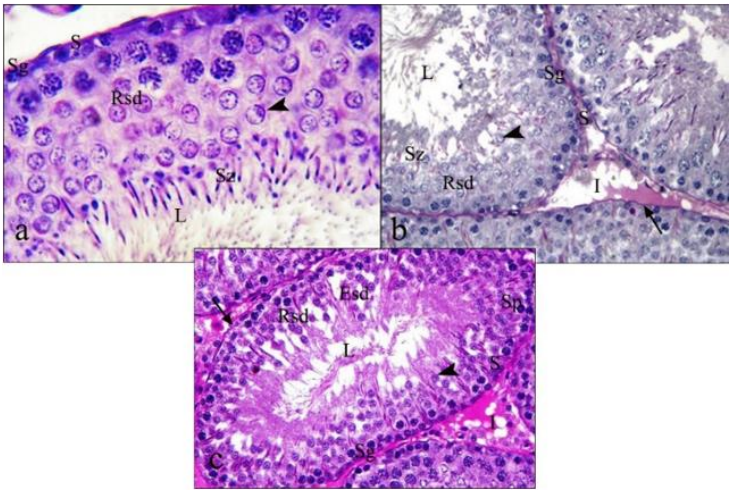
When comparing the semi-thin sections taken from the testes of rats in the 40 mg/kg RA-group with those from the control group, several notable differences were observed. In many stages, it was evident that the intercellular distance between basal compartment cells had increased. Additionally, there was an augmentation in the number of dark-stained, granule-like structures within the cell cytoplasm, particularly in both the basal compartment cells and the cells of the adluminal compartment. This increased intercellular distance among basal compartment cells manifested as cell separation in the thin sections (Figure 6a).

The dark-stained granule-like structures in the semi-thin sections were found to possess membranes when examined under an electron microscope. These sections appeared black in electron microscopy and were hence termed "electron-intense." These structures varied in size, with some being small and numerous while others were larger and less numerous in different locations. In thin sections from stage VIII, the structures within the basal compartments ranged from small to large. Notably, thin sections from stages XI and XIV exhibited a greater number of these structures, and they were larger compared to the control group (Figure 6b).

Primary spermatocytes' nucleus and cytoplasm structures appeared normal, particularly during stages VII-XII. Spermatocytes in various stages of meiosis were also observed to be normal in stage XIV (Figure 6c). Deformation in the cistern appearance of the Golgi body was observed in thin sections from stage VI, which belonged to circular spermatid cells undergoing spermiogenesis. Similarly, in thin sections from stages VII and VIII, deformities in the Golgi bodies of round spermatids were evident, consistent with stage VI (Figure 6d).

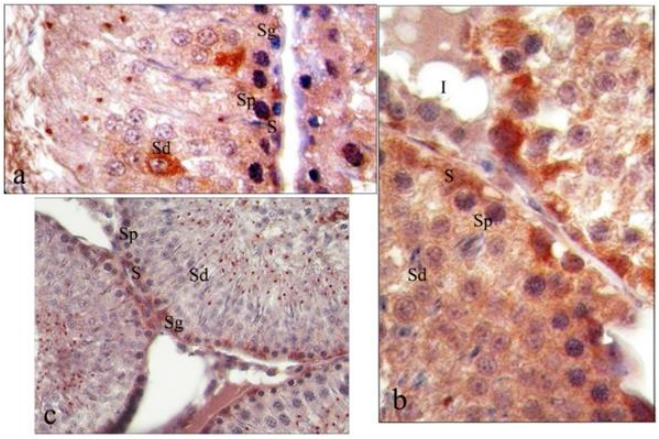
Elongating spermatid cells with oval-shaped heads in stages IX-XI exhibited normal morphology. In thin sections from stages VI and XIV, numerous membrane-enveloped granule-like structures were observed, with these structures being fewer and smaller in volume within the adluminal compartment of the tubule (Figure 6e). In comparison to the control group, there was an increase in the residual material left behind by mature spermatozoa in stage VIII (Figure 6f).

Figure 1: a) Control Group Stage VII Stage; b) 40 mg/kg retinoic acid administrated group VIIth stage; c) 80 mg/kg retinoic acid administrated group VIth stage.



S: Sertoli cell, Sg: spermatogonium, Sp: spermatocyte, Rsd: round spermatid, Esd: elongated spermatid, Sz: spermatozoa, L: lumen, I: interstisium, arrowhead: acrosome, arrow: basal membrane, PAS x100.

Figure 2: a) Control group stage VI; b) 40 mg/kg RA administrated group stage VI; c) 80 mg/kg administrated group stage VI.



S: Sertoli cell, Sg: spermatogonium, Sp: spermatocyte, Sd: spermatid, I: interstisium RARα Immunostaining, ×100.

Figure 3: a) Control group stage VIII; b) 80 mg/kg RA administrated group stage VII. Sz: spermatozoon, RARα İmmunostaining, ×40, ×100 respectively.

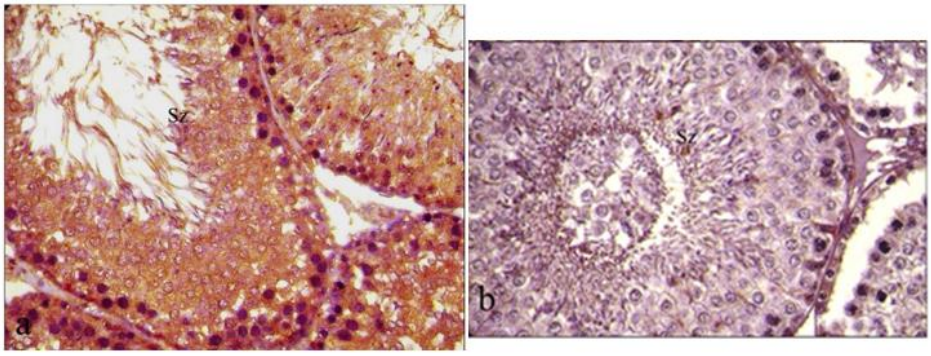


Figure 4: a) Control group stage XIV, b) 80 mg/kg administrated group stage XIV. Sg: spermatogonium, Sp: spermatocyte, Sd: spermatid, L: lumen. RARα İmmunostaining, ×100.

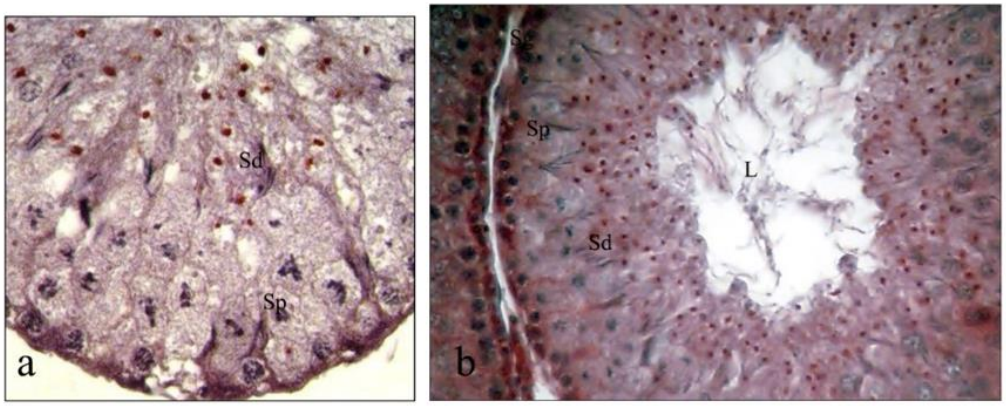
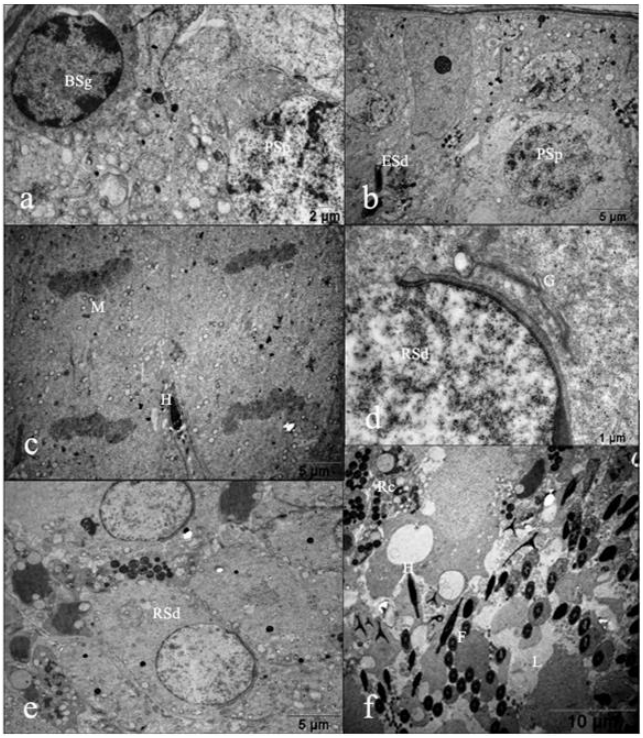
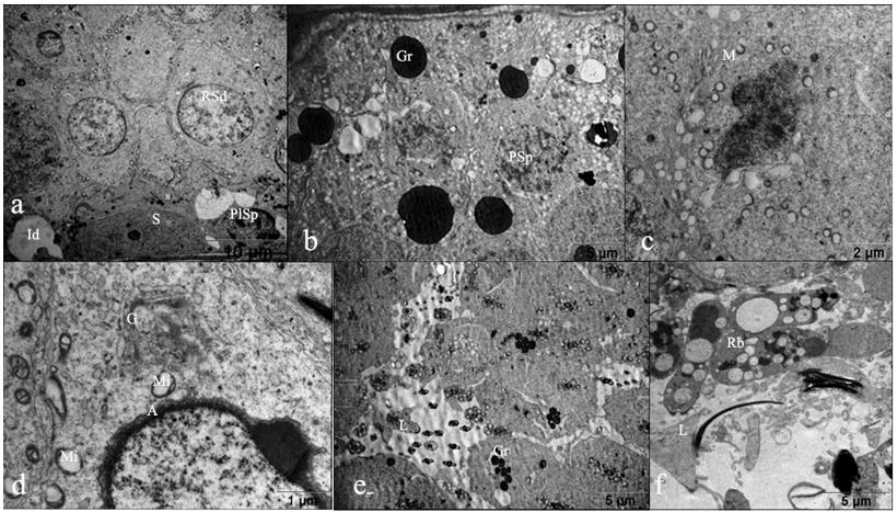


Figure 5: a) Thin section of basal compartment of control group, stage V, b) Thin section of control group, stage V, c) Thin section of Stage XIV meiotic spermatocyte of control group, d) Thin section of stage VII of control group, e) Thin section of stage VIII of control group, f) Thin section of stage VIII of control group.



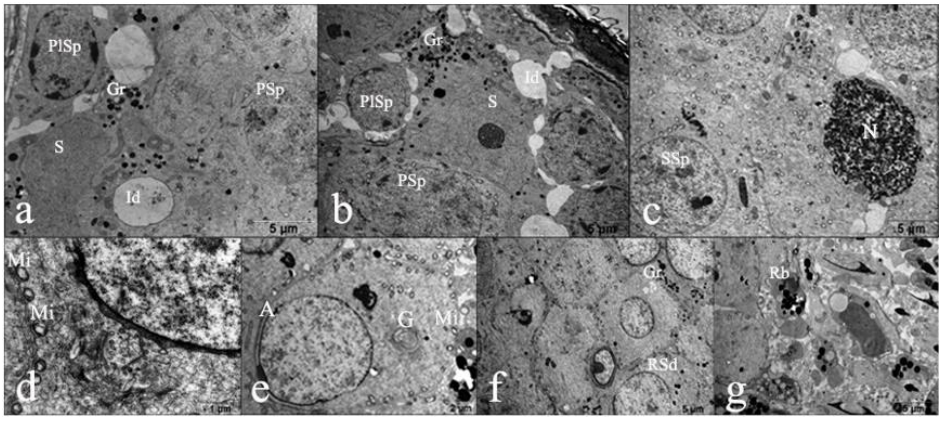
BSg: B-type spermatogonium, PSp: pakiten spermatocyte, ESd: elongated spermatid, H: Head of elongated spermatid (5c), M: Meiotic spermatocyte, Rsd: round spermatid, G: Golgi body, F: Cross section of flagellum of spermatozoon, H: Head of spermatozoon (5f), Rc: residual body, L: lumen.

Figure 6: a) Thin section of stage VII basal compartment of 40 mg/kg RA administrated group, b) Thin section of stage XI basal compartment of 40 mg/kg RA administrated group, c) Thin section of stage XIV meiotic spermatocyte of 40 mg/kg RA administrated group, d) Thin section of stage VII round spermatid of 40 mg/kg RA administrated group, e) Thin section of stage XIV lumen of 40 mg/kg RA administrated group, f) Thin section of stage VIII lumen of 40 mg/kg RA administrated group.



S: Sertoli cell, PlSp: preleptoten spermatocyte, PSp: pachytene spermatocyte, RSd: round spermatid, Id: intercellular distance, Gr: granul, M: Meiotic spermatocyte, G: Golgi body, Mi: mitochondrion, A: acrosome, L: lumen, Rb: residual body.

Figure 7: a) Thin section of stage VI of 80 mg/kg RA administrated group, b) Thin section of stage VIII basal compartment of 80 mg/kg RA administrated group. c)Thin section of stage XIV of 80 mg/kg RA administrated group. d)Thin section of stage VII round spermatid of 80 mg/kg RA administrated group. e) Thin section of stage VIII round spermatid of 80 mg/kg RA administrated group, f) Thin section of stage VIII of 80 mg/kg RA administrated group, g) Thin section of stage VIII lumen of 80 mg/kg RA administrated group



S: Sertoli cell, PlSp: preleptoten spermatocyte, PSp: pachytene spermatocyte, N: necrotic spermatocyte, SSp: seconder spermatocyte, RSd: round spermatid, Id: intercellular distance, Gr: granule, G: Golgi body, Mi: mitochondrion, A: acrosome, Rb: residual body.

Table 1: Qualitative immunoreactivity evaluation of spermatogenetic cell types belonging to control and experimental groups.

	Control					40 mg/kg RA administrated group					80 mg/kg RA administrated group				
Stages	Sertoli cells	Spermatogonia	Spermatocytes	Spermatids	Spermatozoa	Sertoli cells	Spermatogonia	Spermatocytes	Spermatids	Spermatozoa	Sertoli cells	Spermatogonia	Spermatocytes	Spermatids	Spermatozoa
I.	+	+	-	+		+	+	-	+		+	+	-	+	
II-III.	+	+	-	+		+	+	+	+		+	+	+	+	
IV-V.	++	±	-	++		++	+	±	++		++	+	±	++	
VI.	+	+	++	++		++	++	+	+		++	++	+	+	
VII.	++	++	+	±	-	++	++	+	+	+	++	++	++	+	++
VIII.	++	++	++	±	±	++	++	++	+	+	++	++	++	+	++
IX.	±	±	+	-		±	±	±	-		-	-	±	-	
X.	-	-	+	+		-	-	+	+		-	-	+	+	
XI.	-	-	-	+		-	-	-	+		-	-	-	+	
XII.	-	-	-	+		-	-	-	+		-	-	-	+	
XIII.	-	+	-	+		-	+	-	+		-	+	-	+	
XIV.	+	+	±	++		++	++	±	++		++	++	+	++	

(-): no staining, (±): weak immunoreactivity, (+): moderate immunoreactivity, (++): strong immunoreactivity

When comparing the thin sections obtained from rats in the 80 mg/kg-RA group with those from the control group, a significant increase in the intercellular distance between basal compartment cells, as observed in the other experimental group, was noted. Furthermore, the dark-stained granule-like structures seen in adluminal compartment cells were also evident in this group, particularly within basal compartment cells. In thin sections from stage VI of the 80 mg/kg-RA group, the membrane-enveloped granular structures appeared small in size and were numerous, especially in basal compartment cells, coinciding with the extension of the intercellular distance (Figure 7a). Similar deformations were observed in stages VII and VIII, mirroring the observations made in stage VI (Figure 7b).

In contrast, the membrane-enveloped granular structures within the basal compartment appeared small and rare in thin sections from stage XIV when compared to the other experimental group. Both primary spermatocytes, the largest cells within the seminiferous epithelia, and secondary spermatocytes, which can only be observed in stage XIV during various stages of meiosis, displayed a normal morphology. In close proximity to these cells, a necrotic meiotic cell was observed (Figure 7c). Deformation of the Golgi body in round spermatids during stages VI, VII, and VIII was also pronounced in this experimental group, as in the other group (Figure 7d, e). Particularly notable in the basal compartment, membrane-enveloped granule-like structures were small in size and numerous in the cytoplasm of round spermatids during stage VIII (Figure 7f).

Elongating spermatid cells, characterized by their rounding spermatid heads, as well as elongated spermatids, displayed a normal morphological appearance. In comparison to the control group, there was an increase in the number of residual structures left behind by spermatozoa in stages VII and VIII (Figure 7g).

Statistical analysis

The diameters of seminiferous tubules were measured in microns using the Image-Pro Express 4.5 program (Media Cybernetics, Inc., USA). We measured the diameters of ten seminiferous tubules randomly selected from prepared samples of each animal. Four diameter measurements were conducted for each seminiferous tubule, and the arithmetic mean of these measurements was calculated. Subsequently, the obtained values underwent statistical analysis (Table 2a).

Based on the one-way ANOVA, there was a statistically significant difference in the average diameters of seminiferous tubules (P<0.001). Subsequent paired comparisons were conducted using the Dunnett T3 test following the unilateral variance analysis. The results of this test revealed a statistically significant difference when comparing the 80 mg/kg-group with the other groups (P<0.001). However, no statistically significant difference was observed when comparing the 40 mg/kg-RA group with the control group (P=0.147) (Table 2b).

Table 2A: Seminiferous tubules diameter measurement analysis of control and experimental groups.

Group	Mean	SD	n
Control	277.46	35.49	113
40 mg/kg	266.95	45.31	116
80 mg/kg	204.32	36.73	117
Total	249.20	50.96	346

SD: Standard Deviation, One-Way ANOVA, P<0.001

Table 2B: Pairwise comparison of seminiferous tubules diameter means between control and experimental groups with Dunnett T3 test.

Group	Control	40 mg/kg
40 mg/kg	0.147	
80 mg/kg	<0.001	<0.001

Dunnett T3 test, The Dependent Variable: Tubulus Diameter

Discussion

RA, the active metabolite of Vitamin A, plays a crucial role in various essential physiological processes within the body. It serves as a vital signal molecule for normal fetal development, cell proliferation, and differentiation [14]. Vitamin A metabolism is also pivotal for proper spermatogenesis, requiring precise regulation of RA availability. This regulation is essential for spermatogonial differentiation, maintaining the blood-testis barrier function, initiating meiosis, and facilitating proper spermiation [15]. Research has indicated that the highest expression of RARα occurs in round spermatids during stage VIII of the spermatogenetic cycle in adult rats. During stages IX to XI, RARα is predominantly found in the nuclei of elongating spermatids rather than elongated ones, and it is also present in

germ cells undergoing prophase of meiosis, with lower expression in Sertoli cells [16]. The same study emphasizes the role of RARα in Sertoli cells during testis development and its impact on the transformation of round spermatids to elongating spermatids during the meiosis stage of spermatogenesis.

In our study, where we examined RARα immunoreactivity, we observed that Sertoli cells and spermatogonia displayed either moderate or strong staining intensity in stages I-VIII. However, in stage IX, they exhibited weak staining. By stage XIV, all cells displayed staining. Spermatocytes in stages VI-X and spermatids, except for stage IX, exhibited either moderate or strong staining, while spermatozoa in stage VIII showed weak staining.

When a testis becomes completely deficient in RA, the only germ cells found within the seminiferous tubules are undifferentiated spermatogonia. However, when RA is reintroduced into this environment, spermatogenesis resumes normally, albeit in a synchronized manner [17-18]. A recent study has demonstrated that a reduced RA environment within the testes compromises the integrity of the blood-testis barrier and leads to an increased number of meiotic defects, both of which negatively impact fertility [19]. Targeted mutagenesis of the RARα gene has revealed its significant role in spermatogenesis. While cells in all stages of spermatogenesis were still present in RAR-/- testes, there was an elevated occurrence of degenerating pachytene spermatocytes and a temporary developmental arrest in step 8–9 spermatids during the first wave of spermatogenesis.

Additionally, a delay in the onset of the second wave and a temporary arrest in preleptotene to leptotene spermatocytes were observed in the first, second, and third waves. On another note, issues were reported regarding the alignment of spermatozoa in the lumen during stage VIII of the mutant phenotype. In vivo BrdU labeling indicates a significant decrease in germ cell proliferation in both juvenile and adult RARα-/- testes, confirming a halt in spermatids at steps 8 and 9. Consequently, retinoid signal transduction through RARα is deemed crucial for the synchronous progression of spermatogenesis and the formation of the cellular body [20].

In a study conducted by Boulogne et al. [21], the cellular distribution of RAR and RXRs in rats was examined through immunohistochemistry from fetal day 13.5 to postnatal day 8, with comparisons made to the findings in adult rat testes. RARα exhibited pronounced staining in the interstitial connective tissue on fetal day 14.5 and in gonocytes from fetal day 20.5 until postnatal day 8. By the eighth postnatal day, nuclei of all cell types displayed a faint RARα staining. The immunostaining of these receptors predominantly appeared in the cytoplasmic regions of fetal and neonatal testicles, whereas it was notably localized within the nuclei of adult testicles. In our study, however, RARα immunoreactivity was observed as nuclear staining in some spermatogenetic cells, although it was generally observed as cytoplasmic staining.

In a study, it was noted that the rate of spermatogenesis and the diameter of seminiferous tubules exhibited a significant decrease compared to the control group when rats were intraperitoneally administered 6 mg of 13-cis-RA three times a week for 6 weeks [2]. In contrast, the study conducted by Livera et al. [22] introduced selective agonists and antagonists of RARs or RXRs into an organotypical culture system to discern which receptors of RA influenced Leydig, Sertoli, and germ cell development. It was determined that, aside from RAR β predominantly affecting Sertoli cell proliferation, all the effects of RA on fetal and neonatal testicle development were mediated by RAR α. Similar to its RA agonist, RARα disrupted the arrangement of testis cords that had been established on the 14.5th postnatal day and reduced the diameter of testis cords cultivated on the third postnatal day. When comparing the average seminiferous tubule diameters of testis sections between our control and experimental groups, the decrease observed in the 80 mg/kg-RA group was statistically significant compared to both the control group and the 40 mg/kg-RA group.

It has been reported that oral administration of a pan-RAR antagonist inhibited spermatogenesis in mice even at low doses (2.5 mg/kg for 4 weeks) with no discernible side effects other than abnormal testicular histology. Importantly, the impaired spermatogenesis and induced sterility were reversible. Such an impact on fertility suggests that testes are highly sensitive to disruptions in retinoid signaling, and these receptors could be potential targets for pharmacological interventions in male contraception [23]. In a related study [24] by the same research team [23], the effects of daily doses as low as 1.0 mg/kg were examined over dosing periods of 4, 8, and 16 weeks. In all regimens, 100% sterility was observed, with fertility being restored upon discontinuation of the drug treatment, even after 16 weeks. There were no changes in testosterone levels in these males, and the offspring examined from two of the recovered males were healthy and fertile, with normal testicular weight and histology.

Snyder et al. [4] reported that exogenous RA leads to germ cell apoptosis, particularly in type A spermatogonia, and the loss of round spermatids in stages VII and VIII. In another study conducted by Gençoğlan and Tosun [3], which aimed to examine the dose- and time-dependent effects of 13-cis-RA on spermatogenesis in rats, three groups were formed. The experimental groups were daily administered 1 mg/mL and 2 mg/mL of isotretinoin for 21 days, and they exhibited an increase in p53-positive cells compared to the control group. According to the conclusions of this study, it was suggested that long-term treatment with high doses of retinoids could be employed as a method of birth control for men. On the contrary, a study conducted by Ismail et al. [25] reported that rats with vitamin A deficiency experienced testicular deterioration, spermatogenetic cycle arrest at stage VIII, cell apoptosis, and the disappearance of many germ cells at various stages of differentiation. In our study, the observed narrowing in the seminiferous tubule epithelium, possibly attributed to germ cell loss, aligns with the findings of the study mentioned above.

Numerous studies have underscored the pivotal role of RA in germ cell differentiation [26-27]. In a study conducted by Anderson et al. [26] involving juvenile rats of inbred C57BL/6 genetic origin, it was highlighted that the gene Stra8 was essential for initiating meiosis in testis germ cells. Stra8 serves as a distinct cytoplasmic factor in vertebrates, expressed by germ cells in response to RA. The expression of Stra8, a crucial factor for successful meiosis in spermatogenesis, is directly linked to

the presence of RA. Abdelghani et al. [28] identified Stra8 transcripts on the basal surface of seminiferous tubules through their in situ hybridization (ISH) analyses. In the same study, the distribution of this protein in the cryostat sections of adult rat testis was demonstrated at the immunoelectron microscopic level using anti-Stra8 antibodies. Intensive immunoperoxidase staining was also observed in the cytoplasm of germ cells in contact with the basal lamina.

In a study by Zhou et al. [27] aimed at examining the effects of exogenous RA, 8-day-old rats were injected with 350 µg of all-trans RA, while normal adult rats received 750 µg of it. The peak expression of Stra8 mRNA correlated with the onset of meiosis in postnatal testicles. In this study, the earliest detection of Stra8 protein in gonocytes was on postnatal day 5. The expression of Stra8 protein in neonatal testes was not consistent among spermatogonia, potentially indicating the precursor stage of asynchronous spermatogenesis. The highest levels of Stra8 mRNA and protein in seminiferous epithelia were found between stages VI-VIII. The Stra8 protein was identified in certain type A and B spermatogonia, preleptonen spermatocytes, and early leptotene spermatocytes. In vitamin A-sufficient adult rats, RA induced stra8 mRNA expression rather than retinol. In adult spermatogonia, RA stimulated the expression of the Stra8 protein, confirming its role in spermatogonial differentiation. Additionally, RA increased the number of preleptotene spermatocytes, indicating heightened synchronized premeiotic DNA replication. All the studies mentioned above investigating Stra8 transcript and protein induction by retinoic acid and their role in meiosis initiation yielded findings parallel to our study, which also concluded that RA is necessary for the initiation of meiosis, as evidenced by the increase in basal compartment cells in stage VI when the first meiosis begins in rats, based on the immunohistochemical analysis of the RARα protein—one of the nuclear receptors for RA.

Chung et al. [29] conducted a study examining the effects of defective retinoid signal transduction on cell-cell interactions in rats. They demonstrated that hypertonic fixation treatment of RARα-deficient testis tubules disrupted the integrity of Sertoli cell barriers, leading to abnormal intercellular connections during the transition from the basal to adluminal compartments in stain-transfer experiments. This study raises the possibility that the defective spermiogenesis observed in RARα-deficient testicles may result from the deficient cyclic expression of structural RA components, inadequate regulation of connexin-40 within cells, and delayed involvement of zona occludens-1 in Sertoli cell junction complexes.

In a study by Russell et al. [30], cytochalasin D was used to disrupt the actin filaments, which are essential cytoskeletal components of Sertoli cells, affecting spermatids. It was reported that this treatment led to an 88% reduction in the ectoplasmic specialization of the head section of round spermatids in stage VIII compared to the control group. The study also suggested that cytochalasin D treatment caused Sertoli cells to detach from round spermatids, particularly in areas where ectoplasmic specialization was lost on the Sertoli cell surface. Actin in the ectoplasmic specialization area played a significant role in cell-cell interactions. Following cytochalasin D treatment, there was a 5.8-fold increase in the Sertoli cell basal surface orientation of spermatid acrosomes in stage VIII, with the ectoplasmic specialization area playing a crucial role in this orientation.

Taking the findings of these studies into account collectively, it is evident that the RA administered to rats through gavage disrupted Sertoli cell junction complexes, resulting in an increased intercellular distance. This, in turn, accelerated spermiation and led to the accumulation of residual material in the lumen during stages VII-VIII.

In a study conducted by Wu et al. [31], they observed a noteworthy change in the Golgi body of a human glioma cell culture that had been exposed to all-trans RA. Specifically, the Golgi body disappeared, and perinuclear vacuolization occurred. This led to the recognition of the possibility that retinoids could directly influence intracellular traffic by affecting the Golgi body.

In light of this study and the electron microscopic findings in our own research, it is worth noting that the Golgi body in round spermatids at stages VI, VII, and VIII in the experimental groups exhibited a distinct cysterna-like deformation, particularly in the cytoplasmic region near the nucleus.

In a study conducted by Kastner et al. [32] on RXRβ mutant rats, electron microscopy revealed abnormalities in epididymal spermatozoa. Specifically, mutants exhibited an increased occurrence of acrosomes that had detached from the nuclear membrane compared to the wild type, and some spermatozoa lacked acrosomes altogether. It was proposed that these abnormalities, more prevalent in mutant spermatozoa, hindered the proper binding of the acrosomal membrane to the nucleus. Additionally, the large and round vacuoles located in the periphery of the seminiferous tubules in the testes were found to be highly osmophilic in semi-thin sections, indicating their lipid content.

In contrast, electron microscopy revealed that these lipid droplets were devoid of membranes within the Sertoli cell cytoplasm. In our study, we observed granular structures resembling lipid droplets in the basal compartments of the seminiferous tubules in semi-thin sections. However, in electron microscopy examination, these structures were observed to be enveloped by a membrane. Notably, these structures were widespread in basal compartment cells and showed an increased prevalence in the experimental groups.

Conclusion

In conclusion, when we integrate these observations with the results of our study, several key points emerge. Firstly, the impact of exogenous RA on the adult rat testis appears to be dose-dependent. This dosing effect potentially leads to a reduction in the diameter of seminiferous tubules due to germ cell loss. Secondly, there is an indication that the cellular distribution of RARα protein may undergo alterations, influencing its immunoreactivity strength and potentially playing a pivotal role in the initiation of meiosis. Lastly, it is plausible that this mechanism also affects intracellular traffic, possibly through its influence on the Golgi body.

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Results of the laparoscopic lateral suspension and laparoscopic sacrocolpopexy techniques done for uterine prolapse

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Ethics Committee Approval
The study was approved by the Clinical Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçin City Hospital with the registry number 2020/0421 on July 1, 2020.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Sacrocolpopexy is considered the gold-standard surgical treatment for patients with symptomatic uterine prolapse. This technique can be performed using a laparoscopic approach. Laparoscopic lateral suspension has emerged as a new alternative pelvic organ prolapse surgery method. This study aims to compare the postoperative anatomical improvement and sexual function outcomes in patients who underwent laparoscopic sacrocolpopexy (Group 1) versus laparoscopic lateral suspension (Group 2) for pelvic organ prolapse at our institution.

Methods: Group 1 consisted of 14 patients, while Group 2 comprised seven patients. Relevant data were collected using the Turkish-validated Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), A Simple Questionnaire to Screen for Sexual Dysfunction, and the Pelvic Organ Prolapse Quantification System (POP-Q) questionnaires.

Results: There was no statistically significant difference between Group 1 and Group 2 in terms of the preoperative stage of uterine prolapse (2.6 (0.8) vs. 2.7 (0.7) [P=0.534]). The postoperative period was significantly longer in Group 1 compared to Group 2 (1,014.7 (348.8) days vs. 598.4 (276.5) days [P=0.013]). In the POP-Q evaluation, point C was measured as -6.6 (1.1) cm in Group 1 and -5.2 (1.5) cm in Group 2, indicating a statistically more proximal location (P=0.037). The total vaginal length was greater in Group 1 than in Group 2, but this difference was not statistically significant (8.7 (1.2) cm vs. 8.1 (1.3) cm, [P=0.343]). There was no statistical difference between the groups in terms of uterine prolapse stages and sexual function during the follow-up period.

Conclusion: Laparoscopic lateral suspension is an alternative method for patients with uterine prolapse, offering comparable anatomical and sexual outcomes to laparoscopic sacrocolpopexy.

Keywords: anatomical improvement, laparoscopic lateral mesh suspension, laparoscopic sacrocolpopexy, pelvic organ prolapse, sexual function

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Introduction

Pelvic organ prolapse is characterized by the displacement of pelvic organs from their normal anatomical position. The uterosacral and cardinal ligaments, endopelvic fascia, and levator ani muscles provide essential anatomical support for the vaginal apex [1]. Pelvic organ prolapse can manifest as either asymptomatic or with symptoms such as pelvic pressure, a sensation of vaginal fullness, urinary retention, difficulties with defecation, or symptoms of sexual dysfunction. Surgical reconstruction is the recommended treatment for symptomatic patients, involving the repeated suspension of the vaginal apex as well as repair of the anterior or posterior vaginal walls.

Abdominal sacrocolpopexy has been widely recognized as the gold standard for surgical treatment of uterine prolapse [2]. In 1995, Wattiez et al. [3] introduced laparoscopic sacrocolpopexy as an alternative method based on the abdominal promontofixation technique. Subsequently, numerous studies have compared laparoscopic sacrocolpopexy with the abdominal approach [4–6].

Laparoscopic lateral suspension was initially described by Dubuisson et al. [7] in 1998 and has since been recognized as a viable alternative to sacrocolpopexy [7–9]. This technique involves placing a T-shaped polypropylene mesh, which is threaded through a subperitoneal tunnel created parallel to the ovarian vessels, connecting the lateral vaginal fornix to the lateral abdominal wall using a laparoscopic approach. Consequently, the prolapsed pelvic organs are effectively suspended [10].

We hypothesize that laparoscopic lateral suspension could be an alternative approach for treating pelvic organ prolapse. This study, conducted at a tertiary center, aimed to compare the levels of anatomic correction and sexual function outcomes between patients who underwent laparoscopic lateral suspension and those treated with laparoscopic sacrocolpopexy.

Materials and methods

We obtained approval from the Ethics Committee at Göztepe Prof. Dr. Süleyman Yalçin City Hospital Clinical Ethic Committee (registry number: 2020/0421, approval date: July 1, 2020). Patient data were extracted from the hospital's automated registry system. Between January 1, 2016 and December 31, 2019, we identified 21 patients who underwent laparoscopic (L/S) sacrocolpopexy and 14 patients who underwent L/S lateral suspension at our clinic. Patients who declined to participate in the study, those whose contact information could not be obtained, non-Turkish speakers, individuals who had undergone urogynecologic repeat surgery, those with diabetic neuropathy, and patients with advanced gynecologic cancer were excluded from the study.

We provided clear and understandable information to the patients who agreed to participate in the study and obtained their written consent. All procedures were conducted following ethical guidelines and the principles outlined in the Declaration of Helsinki.

L/S sacrocolpopexy was designated as Group 1, with 21 patients initially included. However, only 14 patients from Group 1 were ultimately included in the study. The exclusion of seven patients occurred due to incorrect phone numbers for three patients, one patient residing outside the city, and three patients declining to participate. Similarly, L/S lateral suspension was classified as Group 2, comprising 14 patients. However, only seven patients from Group 2 participated in the study. This reduction was attributed to one patient with an incorrect phone number, three patients residing outside the city, and three patients declining to participate.

After collecting the general demographic data of the patients, we administered a questionnaire designed to enable participants to provide accurate and comfortable responses. The patients completed the "Turkish-validated PISQ-12 Questionnaire" and the "Simple questionnaire to screen sexual dysfunction" forms. In the case of an illiterate patient among the participants, the clinician read the questionnaire items aloud clearly and understandably.

The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 (PISQ-12) is a validated, self-administered questionnaire designed to assess sexual function in women with pelvic prolapse and/or urinary incontinence [11]. It consists of 12 questions, covering emotional factors in items 1–4, physical factors in items 5–9, and partner-related issues in items 10–12. For inclusion in the study, questionnaires required a minimum of ten answered questions; otherwise, they were excluded. The questionnaire allows for comparing total scores and scores in specific sections [11]. For our study, we utilized the validated Turkish version of this questionnaire [12].

Questions 1–4 in the questionnaire employ a reverse Likert scale, where a score of 4 is assigned to 'always' and 0 points to 'never.' Questions 5-12 use a regular Likert scale, with 0 points for 'always' and 4 points for 'never'. In this questionnaire, higher scores indicate better sexual activity, with a maximum possible score of 48 [12].

The "Simple questionnaire to screen sexual dysfunction" is a concise questionnaire consisting of three items, designed to be quickly administered by any physician to assess sexual dysfunction in individuals. The original questions were translated into Turkish while maintaining contextual integrity. Participants were asked the following questions: "1. Are you sexually active? 2. Do you experience any problems during sexual activity? 3. Do you feel pain during sexual activity?" [13]. Each item in the questionnaire offers a choice between 'yes' or 'no' responses.

After completing the questionnaire, a POP-Q evaluation was conducted with the participant in the dorsolithotomy position following voluntary bladder emptying. Measurements were taken using ring forceps scaled in centimeters and uni-valve speculums. Initially, measurements of the genital hiatus (gh), perineal body (pb), and total vaginal length (Tvl) were obtained in a neutral position, ensuring participants were comfortable without straining [1]. Subsequently, anterior and posterior measurements were taken by placing uni-valve speculums on the opposite vaginal wall. Measurements including Aa, Ba, C, Ap, Bp, and D adhered to the original definitions [1]. The distal side of the hymen was assigned a "+" value, while the proximal side was assigned a "-" value. Quantitative results were recorded in a 3-by-3 grid format.

Patients without any prolapse (Aa, Ba, Ap, and Bp points measured as -3 cm, C and D points between Tvl and 2 cm less than Tvl) were classified as stage 0. Those with the most distal part of the prolapse, more than 1 cm proximal to the hymen, were categorized as stage 1. Stage 2 encompassed patients with the most distal part between 1 cm proximal and 1 cm distal to the hymen. Patients with a distal part measuring more than 1 cm but 2 cm less than Tvl were classified as stage 3, while those with total prolapse were assigned stage 4 [1]. In our study, any prolapse classified as stage 2 or higher was considered a recurrent prolapse.

Data pertaining to surgical indications, additional surgical procedures, and perioperative complications were extracted from both the hospital records and surgical records.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of the data was assessed using the Shapiro-Wilk test. Continuous data are presented as mean (standard deviation), while categorical data are presented as percentages. Differences in categorical variables between groups were evaluated using the Chi-square test or Fisher's exact test. Unpaired samples were compared using Student's t-test or the Mann-Whitney U test, as appropriate. Statistical significance was set at a two-sided *P*-value of <0.05.

Results

Age, smoking habits, body mass index (BMI), and history of chronic diseases are summarized in Table 1. There was no statistically significant difference between Group 1 and Group 2 in terms of the preoperative stage of uterine prolapse (2.6 (0.8) vs. 2.8 (0.7), [*P*=0.534]). The mean length of follow-up was longer in Group 1 than in Group 2, indicating statistical significance (1,014.7 (348.8) days vs. 598.4 (276.5) days, [*P*=0.013]). There was no need for repeat urogynecologic surgery for any patient. While de novo incontinence did not develop in any patient in Group 1, it was observed in two patients in Group 2 without statistical significance (*P*=0.100).

Table 1: General features and conditions.

Variables	Group 1 (n=14)	Group 2 (n=7)	*P*-value
Age, mean (SD)	42.5 (7.0)	40.1 (6.2)	0.463
Stage of uterine prolapse (Presurgical), mean (SD)	2.6 (0.8)	2.8 (0.7)	0.534
Additional surgery, n (%)	8 (57%)	3 (43%)	0.659
Mean length of follow-up (Day), mean (SD)	1,014.7 (348.8)	598.4 (276.5)	0.013
Perioperative complication, n (%)	0 (0%)	0 (0%)	-
Gravidity	3.5 (2.0-6.0)	2.0 (1.0-3.0)	0.075
Parity	2.0 (2.0-3.0)	2.0 (1.0-2.0)	0.104
Abortion	1.0 (0.0-2.2)	0.0 (0.0-0.0)	0.051
Vaginal birth number, mean (SD)	2.1 (1.0)	1.7 (0.7)	0.368
Preoperative BMI, mean (SD)	25.1 (3.6)	26.5 (4.2)	0.435
Postoperative BMI, mean (SD)	25.8 (3.8)	27.0 (4.6)	0.528
Postmenopausal woman, n (%)	4 (28%)	2 (28%)	0.701
Smoking habits, n (%)	6 (43%)	3 (43%)	0.681
Chronic diseases, n (%)	9 (64%)	2 (28%)	0.183
Need for repeat urogynecologic surgery, n (%)	0(0)	0(0)	-
De novo incontinence , n (%)	0 (0%)	2 (28%)	0.100
Presence of postoperative symptoms, n (%)	8 (57%)	4 (57%)	0.676
Profession (active workpeople), n (%)	6 (43%)	3 (43%)	0.676

In Group 1, complaints of postcoital penile bleeding in the partner of one participant, a feeling of vaginal fullness in two patients, prolapse in two patients, and ongoing urinary incontinence continuing from the preoperative period in four patients were detected. In Group 2, complaints of pain in two patients, de novo incontinence in two patients (one with pain, together), a feeling of vaginal fullness, and prolapse in one patient were observed. There were no statistically significant differences between the groups regarding symptoms (*P*=0.676).

The comparison of anatomical assessment was performed using POP-Q and recurrence rates in the groups (Table 2). In the POP-Q evaluation, point C was measured as -6.6 (1.1) cm in Group 1 and -5.2 (1.5) cm in Group 2, indicating a statistically more proximal location (*P*=0.037). The Tvl in Group 1 was measured longer than that in Group 2 but without statistical significance (8.7 (1.2) cm vs. 8.1 (1.3) cm, [*P*=0.343]).

Table 2: Comparison of POP-Q examination results and recurrence of pelvic organ prolapse.

Variables	Group 1 (n=14)	Group 2 (n=7)	*P*-value
Aa (cm), mean (SD)	-1.7 (1.0)	-2.3 (0.7)	0.227
Ba (cm), mean (SD)	-1.7 (1.7)	-2.6 (0.4)	0.331
C (cm), mean (SD)	-6.6 (1.1)	-5.2 (1.5)	0.037
Gh (cm), mean (SD)	3.8 (0.8)	4.3 (0.7)	0.235
Pb (cm), mean (SD)	4.0 (1.1)	3.3 (0.4)	0.140
Tvl (cm), mean (SD)	8.7 (1.2)	8.1 (1.3)	0.343
Ap (cm), mean (SD)	-2.1 (1.1)	-1.7 (2.0)	0.813
Bp (cm), mean (SD)	-2.7 (0.5)	-1.6 (2.5)	0.147
D (cm), mean (SD)	-7.3 (1.3)	-6.8 (0.8)	0.328
Anterior wall recurrence, n (%)	4 (29%)	1 (14%)	0.624
Posterior wall recurrence, n (%)	4 (29%)	1 (14%)	0.624
Apical recurrence, n (%)	0 (0%)	0 (0%)	-
Recurrence (on a patient basis), n (%)	5 (36%)	2 (28%)	0.572

While there was no apical recurrence in any patient, anterior wall recurrence was detected in four patients in Group 1 and one patient in Group 2. Similarly, posterior wall recurrence was detected in four patients in Group 1 and one in Group 2. On a patient basis, recurrence was detected in five patients in Group 1 and two patients in Group 2 without statistical significance (*P*=0.572).

In the anterior wall evaluation, ten patients in Group 1 presented with stage 0–1 prolapse, and four presented with stage 2 prolapse. In Group 2, six patients presented with stage 0–1 prolapse, and one presented with stage 2 prolapse. No patients in either group had a more severe prolapse detected.

In the posterior wall evaluation, ten patients in Group 1 presented with stage 0–1 prolapse, and four presented with stage 2 prolapse. In Group 2, six patients presented with stage 0–1 prolapse, and one presented with stage 3 prolapse. There were no patients in either group with other stages of prolapse.

In the apical region evaluation, all 14 patients in Group 1 and 2 patients in Group 2 fell into stage 0–1. Although there was no statistically significant difference between the groups in any compartment, the highest stage of prolapse detected in the study was stage 3 in a patient from Group 2. The relevant findings are summarized in Table 3.

When comparing the groups in terms of sexual functions, no statistically significant difference was found (Table 4). One patient who was not sexually active was excluded from the statistical evaluation. The total PISQ-12 score was 30.7 (6.3) in Group 1 and 33.1 (7.8) in Group 2 (*P*=0.481). In both groups, the highest scores were obtained in the physical variables, with scores of 13.2 (3.9) for Group 1 and 16.3 (3.2) for Group 2 (*P*=0.105). In Group 1, 11 patients reported experiencing pain during sexual activity, while in Group 2, four patients reported the same.

Table 3: Pelvic organ prolapse stages according to vaginal compartments.

	Group 1 (n=14)	Group 2 (n=7)	*P*-value
Anterior Wall			0.710
Stage 0	4 (28%)	3 (42%)	
Stage 1	6 (42%)	3 (42%)	
Stage 2	4 (28%)	1 (14%)	
Stage 3	0	0	
Stage 4	0	0	
Apex			0.638
Stage 0	10 (71%)	4 (57%)	
Stage 1	4 (28%)	3 (42%)	
Stage 2	0	0	
Stage 3	0	0	
Stage 4	0	0	
Posterior Wall			0.187
Stage 0	7 (50%)	3 (42%)	
Stage 1	3 (21%)	3 (42%)	
Stage 2	4 (28%)	0	
Stage 3	0	1 (14%)	
Stage 4	0	0	

Table 4: Comparisons for PISQ-12 and Simple Questionnaire.

	Group 1 (n=14)	Group 2 (n=7)	*P*-value
PISQ-12 Questionnaire Score			
Behavioral, mean (SD)	9.0 (2.7)	8.5 (4.3)	0.769
Physical, mean (SD)	13.2 (3.9)	16.3 (3.2)	0.105
Partner related, mean (SD)	8.5 (3.3)	8.3 (2.5)	0.878
Total PISQ score, mean (SD)	30.7 (6.3)	33.1 (7.8)	0.481
Simple Questionnaire			
Sexually active, n (%)	14 (100%)	6 (85%)	0.147
Problem in sexual activity, n (%)	4 (28%)	0 (0%)	0.267
Pain in sexual activity, n (%)	11 (78%)	4 (66%)	0.613

Discussion

The primary symptoms associated with pelvic organ prolapse include feeling fullness and pressure. However, in addition to these, pelvic organ prolapse may also manifest with symptoms such as incontinence and sexual dysfunction. The treatment options for pelvic organ prolapse range from conservative measures like lifestyle modifications, Pesser use, and physical therapy to surgical procedures employing natural tissues or meshes [1]. L/S sacrocolpopexy and L/S lateral suspension are surgical procedures that involve using mesh to treat uterine prolapse.

Two prospective studies assessed the PISQ-12 scores and sexual functions of patients who underwent laparoscopic sacrocolpopexy. In both studies, the postoperative scores were higher than the preoperative scores [14,15]. In our study, the laparoscopic sacrocolpopexy group had a mean follow-up time of 1,014 days, and the average PISQ-12 score was 30.7. These findings indicate lower values compared to the studies mentioned above.

In a study that assessed preoperative and postoperative sexual functions using the Female Sexual Function Index, patients who underwent laparoscopic lateral suspension scored higher in both settings [10]. In our study, the mean follow-up time for the lateral suspension group was 598 days, and the average PISQ-12 score was 33.1. We did not find any studies directly comparing PISQ-12 scores and sexual functions between patients who underwent laparoscopic sacrocolpopexy and those who underwent laparoscopic lateral suspension. Despite using different questionnaires, both methods demonstrated improved scores regarding sexual functions during the postoperative period.

In a systematic review involving 1,066 patients who underwent lateral suspension surgery, the reported rates of surgery-related postoperative complications were as follows: 33 (3.1%), 42 (3.9%), two (0.2%), and eight (0.8%) for Clavien Dindo grades 1, 2, 3a, and 3b, respectively. During the perioperative period, 9 patients experienced bladder injuries, and three patients had bowel injuries. In the postoperative period, 16 patients developed urinary tract infections, 11 patients experienced urinary retention, one patient had pyelonephritis, one patient had a hemorrhage, 16 patients reported pain, one patient had ablation of the lateral suture fixing mesh, ten patients developed vaginal granulation tissue, one patient had a uterovaginal fistula, and one patient required excision of the mesh due to erosion through the vaginal route within the first 30 days [16]. A total of 32 patients (3.1%) experienced mesh erosions, and the erosion rates for the relevant mesh types were as follows: titanium-coated polypropylene, 1.8%; polypropylene, 2.3%; polyethylene, 5.8% [16]. We did not observe any cases of mesh erosion in any of the groups.

Various anatomical success criteria have been used to define the effectiveness of laparoscopic lateral suspension. The success rates for the anterior vaginal wall ranged from 76.2% to 100%, for the apical region from 84.4% to 100%, for the posterior vaginal wall from 75% to 85%, and the overall success rate ranged from 82.7% to 100%. The recurrence rates for the anterior wall ranged from 0% to 9.4%, for the apical region from 0% to 7.4%, for the posterior wall from 1.6% to 20%, and the overall recurrence rates were reported as 5.7% to 20%. The re-operation rate ranged from 0% to 13% [16]. In our study, no secondary urogynecological operations were required, and we did not observe any cases of apical recurrence in either group. The recurrence rates for the anterior and posterior vaginal walls were 29% and 14% for Group 1 and Group 2, respectively.

In the sacrocolpopexy technique, the vaginal wall is anchored to a mesh using the anterior longitudinal ligament. This procedure requires retroperitoneal dissection through the right pelvic wall and presacral dissection, which involves close contact with structures such as the ovarian artery, common iliac artery, sigmoid colon, and presacral venous plexus. A meta-analysis comparing L/S sacrocolpopexy with robotic sacrocolpopexy in 18 studies revealed that after L/S sacrocolpopexy, the mean blood loss was 100.58 ml, the mean operation time was 50.24 min, and the mean rates of intraoperative bladder, bowel, vascular, and ureteral injuries were 3.1%, 1.1%, 0.8%, and 0%, respectively. Additionally, the rates of postoperative mesh erosion, anorectal dysfunction, and sexual dysfunction were reported as 2.7%, 3.2%, and 13%, respectively, following laparoscopic methods [17]. In a study by Baines et al. [18] on L/S sacrocolpopexy using mesh, complications included five cases of vaginal mesh exposure, four cases of suture erosion, six cases of bladder injury, five cases of vaginal buttonholing, one case of intraabdominal hemorrhage, one case of repeat laparoscopy for suspected bleeding without significant findings, one case of bowel injury, three cases of hematomas (one in the vaginal vault and two in the abdominal incision), nine cases of local infection, and one case of incisional hernia. The mean operation time was reported as 90 min (ranging from 27 to 251 min), and the mean hospital stay was 2 days (ranging from 0 to 85 days). Preoperative Point C had a mean value of 1.18 cm, while postoperative Point C had a mean value of -7.3 cm, representing an approximate difference of 8.5 cm [14]. Our study measured the mean values for Point C as -6.6

(1.1) cm and -5.2 (1.5) cm for the L/S sacrocolpopexy and L/S lateral suspension groups, respectively. Vascular injuries, hypogastric plexus lesions, right hypogastric nerve lesions, spondylodiscitis, and lumbar pain were reported in various studies following sacrocolpopexy [8,19–22].

The mean surgery times reported for L/S lateral suspension were 108.8 (29.8), 78.4 (29.7), and 245 (45) min in three different studies [7,10,23]. In studies on sacrocolpopexy, the mean surgery times ranged from 50.24 to 90 min [17,18]. Another study found a statistically significant difference in mean surgery times between experienced operators and trainees, with 178 min versus 251 min, respectively. However, there were no significant differences in perioperative complications and short-term anatomical results between the two groups [24].

Limitations

This study has several limitations, including the retrospective collection of patient data, a small sample size, variations in the length of follow-up, differences between the groups, operations performed by different surgeons, and a focus on comparing short-term results. However, this study may still hold advantages due to the scarcity of research on comparing postoperative improvements in prolapse and sexual functions between patients undergoing L/S sacrocolpopexy and L/S lateral suspension. Nevertheless, there is a need for randomized prospective studies and meta-analyses to compare both short-term and long-term outcomes.

Conclusions

Abdominal sacrocolpopexy is widely accepted as the gold standard surgical treatment for uterine prolapse and can be safely performed using a laparoscopic approach. L/S lateral suspension has emerged as a newer alternative method for treating uterine prolapse. In the present study, we found that laparoscopic lateral suspension surgery demonstrated comparable anatomical improvement, sexual function outcomes, rates of de novo incontinence development, and postoperative symptom profiles in patients within the same age groups and with similar preoperative levels of uterine prolapse. There were no significant differences between the groups regarding PISQ-12 scores, dyspareunia, or recurrence. Except for point C, there were no statistically significant differences between the groups regarding POP-Q reference points. Point C was measured more proximally in L/S sacrocolpopexy than in L/S lateral suspension. In conclusion, both L/S lateral suspension and L/S sacrocolpopexy yielded similar short-term anatomical and sexual outcomes. However, considering that L/S lateral suspension is an easier technique to learn and involves a safer intraoperative dissection plan, it may be preferred over L/S sacrocolpopexy.

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New trends associated with disease activity in patients with ulcerative colitis

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Ethics Committee Approval
The study was approved by the Clinical Ethics Committee of Celal Bayar University Medical Faculty (April 18, 2018 -E.no.10-008CC). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The severity and extent of ulcerative colitis (UC) guide us in determining the treatment method for each case. It has been suggested in the literature that high neutrophil-lymphocyte and platelet-lymphocyte ratios can serve as markers of active ulcerative colitis. This study retrospectively analyzes the relationship between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with clinical activity indices and endoscopic activity indices in predicting disease severity in patients with ulcerative colitis. There are few studies in the literature regarding the relationship between platelet-lymphocyte ratio (PLR) and disease activation in ulcerative colitis. This study contributes to the follow-up and outcomes of these patients, as there is a lack of sufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and worldwide.

Methods: This study is a population-based, single-center, case-controlled study. It was conducted by retrospectively analyzing the hospital information system for data recorded during the routine diagnosis and treatment of ulcerative colitis patients followed and treated at Celal Bayar University Medical Faculty Gastroenterology Division between January 2014 and December 2021. A total of 135 patients with ulcerative colitis were included in the study. The patients were divided into 2 groups, active disease and disease in remission, based on clinical activity indices and endoscopic activity indices. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), white blood cell (WBC), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) levels were checked during routine follow-up of patients with ulcerative colitis. These values were recorded at the first presentation to the hospital and 3 months after treatment.

Results: Laboratory values at presentation were compared with those at the third month of treatment in a group of 113 patients with UC in remission: NLR (5.529 (3.485) and 4.374 (2.335), [P<0.001]), erythrocyte sedimentation rate (26.81 (20.42) and 21.78 (19.32), [P=0.015]), C-reactive protein (4.087 (6.729) and 1.696 (3.525), [P<0.001]), and white blood cell count (9,864 (3,514) and 8,067 (1,927), [P<0.001]) were found to be lower than the baseline values. As expected, decreases in inflammatory markers were observed in patients in remission. In a group of 22 patients with active disease, values at presentation were compared with those at the third month of treatment: neutrophil count (8,508 (2,908) and 9,646 (3,265), [P=0.037]) and platelet count (289,591 (95,123) and 323,364 (127,647), [P=0.010]) were found to be high. Similarly, ESR (19.63 (15.43) and 27.89 (21.11), [P=0.036]) was found to be high. These values were higher in active disease compared to the time of admission.

Conclusion: In our study, neutrophil-lymphocyte ratios and platelet-lymphocyte ratios were significantly higher in patients with active ulcerative colitis. The level of inflammatory markers in ulcerative colitis patients at the time of diagnosis and in the early stages of the disease is helpful in predicting the course of the disease, and this was shown to be related to clinical, endoscopic, and laboratory indices. These inflammatory markers can predict disease activity alone or in combination. However, a threshold value could not be calculated due to the insufficient number of patients, and thus, more comprehensive prospective studies are needed.

Keywords: ulcerative colitis, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, C-reactive protein, erythrocyte sedimentation rate

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that develops due to diffuse inflammation of the colonic mucosa. It is characterized by periods of activation and remission and by ulcers in the colonic mucosa. The disease typically has an insidious course. The proposed hypothesis for the etiopathogenesis of UC is the development of an immunologic disorder in genetically susceptible individuals, influenced by environmental and microbial factors [1].

The course of UC is related to disease activity, the risk of inflammation progression, the number of relapses, the need for surgery, and mortality. Parameters such as increased neutrophil count, increased neutrophil-lymphocyte ratio (NLR), increased platelet-lymphocyte ratio (PLR), increased C-reactive protein (CRP), increased erythrocyte sedimentation rate (ESR), along with decreased hemoglobin (Hb) and decreased albumin, indicate disease flare. Additionally, mucosal inflammation is frequently used to monitor the disease and evaluate treatment response [2-4].

In the recent literature, parameters such as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), obtained from full blood count parameters, have been investigated as markers of inflammatory disease [5,6]. The ratio of these two subgroups is used as an inflammation marker because the physiological response of leukocytes to stress leads to an increase in neutrophil count and a decrease in lymphocyte count [7,8]. Thrombocytosis occurs as a result of stimulation of megakaryocytes by proinflammatory cytokines [9]. The association of thrombocytosis with clinical prognosis, as demonstrated in relevant studies, can be explained by the high platelet count being an indicator of the severity of inflammation.

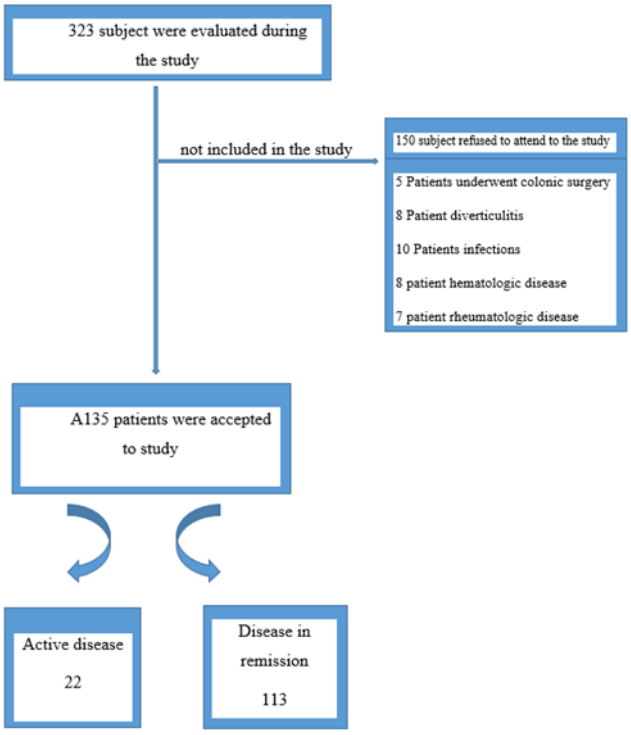
While the previous ideal treatment of ulcerative colitis focused on improving disease symptoms, achieving remission, and maintaining that remission period, the current ideal treatment aims to induce disease remission, prevent exacerbations, reduce the need for hospital admission, and provide long-term symptomatic and deep mucosal improvements without corticosteroids and with minimal need for surgery [10].

In this study, we retrospectively analyzed the relationship between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with clinical activity indices and endoscopic activity indices in predicting disease severity in patients with ulcerative colitis. There are few studies in the literature that consider the relationship between platelet-lymphocyte ratio (PLR) and disease activation in ulcerative colitis. This study contributes to the follow-up of these patients and the outcomes obtained, as there is a lack of sufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and worldwide.

Materials and methods

Our study is a population-based, single-center case-control study. We conducted this study by retrospectively analyzing the hospital information system for information recorded during the routine diagnosis and treatment of patients with ulcerative colitis. These patients were followed and treated at the Gastroenterology Division of Celal Bayar University Medical Faculty and presented to our hospital between January 2014 and December 2021. A total of 135 patients with ulcerative colitis were included in the study. The patients were divided into two groups, active disease and disease in remission, based on clinical activity indices and endoscopic activity indices (Figure 1). Cases with concomitant diseases such as infection, hematologic disease, rheumatologic disease, or malignancy that would cause an increase in serum neutrophil, leukocyte, and platelet values were excluded from the study.

Figure 1: Flow diagram of the study



Consent for the study was obtained from the Celal Bayar University Medical Faculty Ethics Committee (April 18, 2018-E. no.10-008CC).

During routine follow-up of ulcerative colitis patients, we evaluated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), white blood cell (WBC) count, platelet count, lymphocyte count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). We evaluated these parameters separately for each patient at their initial presentation to the hospital and at the 3-month follow-up after starting appropriate treatment. Based on their clinical condition and endoscopic findings, we divided the patients into two groups: the patient group in remission and the active patient group unresponsive to treatment.

We compared the neutrophil count, platelet count, lymphocyte count, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, hemoglobin, sedimentation rate, CRP values, clinical findings, endoscopic findings, and clinical and endoscopic activity indices of the patients at their initial presentation to the hospital (control 1) with the same parameters at the 3-month follow-up after starting treatment (control 2).

Multiple activity indices were used to evaluate disease activity. We used the Truelove-Witts classification, calculated with clinical and laboratory findings, and the Rachmilewitz Endoscopic Activity Index, which includes endoscopic findings, in the study [11,12].

Statistical analysis

We used the SPSS 22.0 program for statistical evaluation. Descriptive statistics included mean, standard deviation, median, minimum, and maximum values for continuous variables and percentage values for discrete variables. We tested the conformity of numerical variables to a normal distribution using the Shapiro-Wilk test. Categorical variables were presented as frequency and percentage, and numerical variables were presented as mean and standard deviation values. We analyzed the relationship between two independent categorical variables using the chi-squared test. We compared the means of repeated measurements using the dependent sample t-test for variables that showed a normal distribution and the Wilcoxon signed rank test for variables that did not show a normal distribution. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 135 UC patients who were followed at the Gastroenterology Division of Celal Bayar University Medical Faculty between January 2014 and December 2021 were included in the study. Of the 135, 76 (56.3%) were male and 59 (43.7%) were female, with a mean age of 45 (5). The demographic characteristics of the patients are shown in Table 1.

Table 1: Demographic characteristics of the patients

	UC patients in remission with treatment		Active UC patients not in remission with treatment	
	n	%	n	%
Gender				
Female	49	43	10	45
Male	64	57	12	55
Age range				
18-28	15	13.5	4	18.2
29-39	34	30	6	27.3
40-50	23	20.3	4	18.2
51-61	24	21.2	3	13.6
62-72	12	10.6	3	13.6
73+	5	4.4	2	9.1
Total	113	100	22	100

In the patient group in remission with treatment, the mean neutrophil count was 9,864 (3,514) at first presentation and 8,067 (1,927) after 3 months of treatment. The mean neutrophil count after treatment was significantly lower than the mean neutrophil count at first presentation (*P*<0.001). The mean platelet count of the same patient group was 318,257 (108,354) at first presentation and 288,310 (90,251) after 3 months of treatment. The mean platelet count after treatment was significantly lower than the mean platelet count at first presentation (*P*=0.001). The mean lymphocyte count of the same patient group was 2,106 (835.4) at first presentation and 2,132 (746.1) after 3 months of treatment. There was no significant difference between the mean lymphocyte counts before and after treatment (*P*=0.340).

In the patient group in remission with treatment, the mean neutrophil-lymphocyte ratio was 5.529 (3.485) at first presentation and 4.374 (2.335) after 3 months of treatment. The mean neutrophil-lymphocyte ratio after treatment was significantly lower than the mean neutrophil-lymphocyte ratio at first presentation (*P*<0.001). The mean platelet-lymphocyte ratio of the same patient group was 174.3 (88.37) at first presentation and 155.6 (81.20) after 3 months of treatment. The mean platelet-lymphocyte ratio after treatment was significantly lower than the mean platelet-lymphocyte ratio at first presentation (*P*=0.027).

In the patient group in remission with treatment, the mean erythrocyte sedimentation rate was 26.81 (20.42) at first presentation and 21.78 (19.32) after 3 months of treatment. The mean erythrocyte sedimentation rate after treatment was significantly lower than the mean erythrocyte sedimentation rate at first presentation (*P*=0.015). The mean CRP of the same patient group was 4.087 (6.729) at first presentation and 1.696 (3.525) after 3 months of treatment. The mean CRP after treatment was significantly lower than the mean CRP at first presentation (*P*<0.001). The mean hemoglobin value of the same patient group was 12.49 (2.129) at first presentation and 12.73 (1.864) after 3 months of treatment. There was no significant difference between the mean hemoglobin values before and after treatment (*P*=0.163). The comparison of laboratory parameters of UC patients in remission with treatment is shown in Table 2.

In the patient group with active UC not in remission with treatment, the mean neutrophil count was 8,508 (2,908) at first presentation and 9,646 (3,265) after 3 months of treatment. The mean neutrophil count after treatment was significantly higher than the mean neutrophil count at first presentation (*P*=0.037). The mean platelet count of the same patient group was 289,591 (95,123) at first presentation and 323,364 (127,647) after 3 months of treatment. The mean platelet count after treatment was significantly higher than the mean platelet count at first presentation (*P*=0.010). The mean lymphocyte count of the same patient group was 2,162 (979.5) at first presentation and 2,552 (1318) after 3 months of treatment. There was no significant difference between the mean lymphocyte counts before and after treatment (*P*=0.108).

Table 2: Comparison of laboratory parameters of UC patient group in remission with treatment

Patient group in remission with treatment	n	First presentation Mean (SD)	After treatment Mean (SD)	*P*-value
Neutrophil count	113	9,864 (3,514)	80,67 (1,927)	**<0.001**
Platelet count	113	318,257 (108,354)	288,310 (90,251)	**0.001**
Lymphocyte count	113	2,106 (835.4)	2,132 (746.1)	0.340
NLR	113	5.529 (3.485)	4.374 (2.335)	**<0.001**
PLR	113	174.3 (88.37)	155.6 (81.20)	**0.027**
Sedimentation	86	26.81 (20.42)	21.78 (19.32)	**0.015**
CRP	100	4.087 (6.729)	1.696 (3.525)	**<0.001**
Hemoglobin	113	12.49 (2.129)	12.73 (1.864)	0.163

In the patient group with active UC not in remission with treatment, the mean neutrophil-lymphocyte ratio was 4.308 (1.563) at first presentation and 4.386 (2.10944) after 3 months of treatment. There was no significant difference between the mean neutrophil-lymphocyte ratios before and after treatment (*P*=0.689). The mean platelet-lymphocyte ratio of the same patient group was 152.4 (65.59) at first presentation and 153.9 (86.17) after 3 months of treatment. There was no significant difference between the mean platelet-lymphocyte ratios before and after treatment (*P*=0.570).

In the patient group with active UC not in remission with treatment, the mean sedimentation rate was 19.63 (15.43) at first presentation and 27.89 (21.11) after 3 months of treatment. The mean erythrocyte sedimentation rate after treatment was significantly higher than the mean erythrocyte sedimentation rate at first presentation (*P*=0.036). The mean CRP of the same patient group was 2.066 (2.434) at first presentation and 2.451 (3.811) after 3 months of treatment. There was no significant difference between the CRP values before and after treatment

(*P*=0.811). The mean hemoglobin values of the same patient group were 12.88 (1.910) at presentation and 13.03 (1.939) after 3 months of treatment. There was no significant difference between the mean hemoglobin values before and after treatment (*P*=0.585). The comparison of laboratory parameters of active UC patients not in remission with treatment is shown in Table 3.

Table 3: Comparison of laboratory parameters of active UC patient group not in remission with treatment

Active patient group not in remission with treatment	n	First presentation Mean (SD)	After treatment Mean (SD)	*P*-value
Neutrophil count	22	8,508 (2,908)	9,646 (3,265)	**0.037**
Platelet count	22	289,59 (95,123)	323,36 (127,647)	**0.010**
Lymphocyte count	22	2,162 (979.5)	2,55 (1318)	0.108
NLR	22	4.30 (1.563)	4.386 (2.10944)	0.689
PLR	22	152.4 (65.59)	153.9 (86.17)	0.570
Sedimentation	19	19.6 (15.43)	27.8 (21.11)	**0.036**
CRP	19	2.06 (2.434)	2.451 (3.811)	0.811
Hemoglobin	22	12.8 (1.910)	13.0 (1.939)	0.585

Discussion

In our study, we analyzed the clinical and laboratory follow-up, as well as endoscopic findings, of 135 patients with ulcerative colitis. We examined their first presentation at our hospital and their control visit after treatment planning to determine their clinical prognosis. We compared laboratory findings, such as hemoglobin, erythrocyte sedimentation rate, CRP, leukocytes, platelets, and lymphocytes, which are inflammatory markers used to identify flare-ups and determine clinical prognosis. Based on endoscopic and clinical findings, we divided the patients into two groups: the "patient group in remission" and the "active patient group not in remission with treatment." We found that certain parameters, such as neutrophil count, platelet count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, erythrocyte sedimentation rate, and CRP values, were related to better clinical prognosis in the patient group in remission. In the active patient group, neutrophil count, platelet count, and erythrocyte sedimentation rate were related to worse clinical prognosis.

Parameters associated with disease activity in ulcerative colitis, such as white blood cells, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), have been studied in the literature. Torun et al. compared NLR in active UC, inactive UC, and control groups and found that NLR was higher in the active group than the inactive group. They also showed a correlation between NLR and white blood cell and ESR values [13,14]. Çelikbilek et al. [15] conducted a study on the neutrophil/lymphocyte ratio in ulcerative colitis patients and found that NLR was associated with active disease. Another study in Turkey on 49 UC patients found a correlation between NLR and active UC [4]. A study in Japan analyzed the correlation between NLR and disease activity as well as response to treatment. They found that pre-treatment NLR values were comparatively high in patients with moderate and severe disease activity who were subsequently started on infliximab [16]. Akpinar et al. [17] conducted a study that investigated the use of an NLR-PLR combination for evaluating endoscopic disease activity in UC. They reported that high NLR or PLR levels could predict active endoscopic disease. Demir et al. [18] published a study in 2015 showing that a higher neutrophil-lymphocyte ratio (NLR) was an indicator of active UC.

Consistent with the literature, our study also found a relationship between neutrophil count and worse clinical prognosis. We observed that the mean neutrophil count of patients in remission was high at presentation to the hospital but decreased after 3 months, as expected. On the other hand, the mean neutrophil count of active UC patients not in remission with treatment was low at presentation to the hospital but increased after 3 months, as expected.

When we analyzed the relationship between NLR and disease activation, we found that the mean NLR values of our patients in remission were high at presentation to the hospital but decreased after 3 months, as expected. The mean NLR values of our patients with active UC not in remission with treatment were low at presentation to the hospital but slightly increased after 3 months, as expected.

Regarding the relationship between platelet-lymphocyte ratio (PLR) and disease activation in ulcerative colitis, there are few studies on this in the literature. However, studies analyzing the relationship between PLR and other diseases have been performed. For example, increased platelet/lymphocyte ratio (PLR) has been reported as an independent risk factor for decreased survival in pancreas and colorectal cancers [19,20]. In the study by Akpinar et al. [17], which included 104 patients with active UC, 104 patients in remission, and a control group of 105 healthy individuals, mean NLR and PLR values in the endoscopically active disease group were higher than those in the group with endoscopic remission.

In this study, we also analyzed the relationship among UC, platelet count, and PLR to contribute to the literature and science. This study actively contributes to the follow-up of these patients and the outcomes obtained, as there are insufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and globally. When we considered the relationship between platelet count and clinical prognosis, we found that the mean platelet count of patients in remission was high at presentation to the hospital but lower after 3 months, as expected. The mean platelet count of patients with active UC not in remission with treatment was low at presentation to the hospital but higher after 3 months.

When we considered the relationship between PLR and disease activation, we found that the mean PLR value in patients in remission was high at presentation to the hospital but lower after 3 months. The mean NLR of patients with active disease not responding to treatment was low at presentation to the hospital, but the control value after 3 months was slightly higher. This could be attributed to the small number of patients with progression.

Overall, our study contributes to the understanding of clinical prognosis in ulcerative colitis and highlights the importance of laboratory markers such as neutrophil count, NLR, platelet count, and PLR in predicting disease activity and treatment response.

Another issue addressed in our study was the association of other inflammatory markers (CRP, erythrocyte sedimentation rate, anemia, etc.) with disease activation. Bengi et al. [21] found anemia in more than half (51.6%) of IBD patients; half of those with anemia were receiving treatment for it. The Truelove-Witts scoring system revealed that ESR is the most commonly used parameter for determining clinical activity. A study conducted in Korea aimed to determine which parameter

was most associated with clinical activity in UC patients. The results of a correlation analysis showed that in cases where there was a discrepancy between ESR and CRP, ESR was found to be more useful in evaluating disease activity in UC patients [22]. Many studies have shown a correlation between CRP and UC disease activity, as well as the severity of the activity. In a study by Solem et al. [3] on UC patients, CRP elevation was found to be correlated with disease activity, ESR elevation, hypoalbuminemia, and anemia.

In 2003, Ece et al. [23] studied 35 UC patients (12 active, 23 inactive) and 36 healthy individuals. Full blood count, routine biochemical workup, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were checked in all individuals. ESR and CRP levels were significantly higher in active cases compared to inactive cases and the control group.

In our study, we analyzed the relationship between CRP and disease activation. We found that while the mean CRP level of patients in remission was high upon presentation to the hospital, the control value 3 months later was low. On the other hand, the mean CRP level of patients with active UC not in remission with treatment was low upon presentation to the hospital, but the control level 3 months later was slightly high. In the patient group in remission, we found a statistical relationship between CRP and disease activation, as reported in many other studies. However, we could not establish this relationship in the active patient group that did not respond to treatment. This absence of a relationship between CRP levels and disease activity in the active UC group may be due to the small sample size of 22 patients.

In a study by Yoon et al., the correlation of ESR and CRP with endoscopic activity was investigated. It was predicted that these markers could be useful in determining activity but would be insufficient in determining remission [25]. In our study, we analyzed the relationship between erythrocyte sedimentation rate (ESR) and disease activation. We found that while the mean ESR value of patients in remission was high upon presentation to the hospital, the control value 3 months later was low. On the other hand, the mean ESR value of patients with active UC not in remission with treatment was low upon presentation to the hospital, but the control value 3 months later was high. In this case, a statistical relationship was shown between ESR and disease activation, as demonstrated in many other studies.

It is believed that hemoglobin value decreases in UC patients due to the frequency of bloody diarrhea, malnutrition, and chronic inflammation. A study by Ibarra-Rodriguez et al. [26] with 45 patients and 15 controls demonstrated a correlation between Hb and hematocrit value and endoscopic disease activity. However, in our study, we could not establish a relationship between mean hemoglobin value and disease activity in either the patient group in remission or the patient group with active UC not in remission with treatment.

Limitations

The limitations of our study include its retrospective nature, the small number of patients, the lack of a healthy control group, and the inability to evaluate disease activity indices together. However, this study contributes to the follow-up of UC patients and the outcomes obtained, as there are insufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and worldwide.

Conclusion

In conclusion, this study investigated the clinical prognostic importance of inflammatory markers and neutrophil/lymphocyte and platelet/lymphocyte ratios in patients with ulcerative colitis. The patients were divided into the patient group in remission and the patient group with active UC not in remission, with treatment based on their clinical and endoscopic findings. The relationship between laboratory parameters and clinical prognosis was investigated in the group in remission, and a relationship between neutrophil count, platelet count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and better clinical prognosis was determined. In the patient group with active UC not in remission with treatment, a relationship was found between worse clinical prognosis and only neutrophil count and platelet count. The small number of patients with active UC not in remission with treatment was cited as a reason for not establishing a relationship between clinical prognosis and PLR and NLR. Based on the patient group in remission, which had an adequate number of patients, it can be concluded that PLR and NLR are effective clinical prognostic markers in UC patients.

When considering other inflammatory markers, both erythrocyte sedimentation rate and CRP were found to be related to better clinical prognosis in the patient group in remission. However, only erythrocyte sedimentation rate was found to be related to worse clinical prognosis in the patient group with active UC who were not in remission with treatment. Since CRP can sometimes lead to errors in determining the clinical prognosis, it can be concluded that erythrocyte sedimentation rate is superior to CRP in determining clinical prognosis.

Based on this information, it is necessary to conduct comprehensive and prospective studies with a larger number of patients to determine the predictive power of inflammatory markers at the time of diagnosis or in the advanced stages of the disease. This will help to popularize the use of these markers in clinical practice by establishing a threshold value.

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Evaluation of anxiety and hopelessness levels in emergency service workers during the COVID-19 pandemic in Turkey

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Ethics Committee Approval
The study was approved by the Amasya University Non-Interventional Clinical Research Ethics Committee (2020/43).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The COVID-19 pandemic led to a significant threat to the lives of individuals, particularly frontline healthcare workers. This brought about negative emotions, such as anxiety and hopelessness. Despite the existence of research evaluating psychiatric symptoms among healthcare personnel during the COVID-19 pandemic, this study is also significant in terms of evaluating and emphasizing the common negative emotions experienced by frontline healthcare workers during the pandemic. This study aimed to evaluate anxiety and hopelessness levels in emergency service workers during the COVID-19 pandemic and to examine these levels in terms of specific variables.

Methods: This cross-sectional study was conducted among emergency service healthcare workers, including doctors, nurses, and healthcare officers working in a training and research hospital from July 10 to August 10, 2020 during the pandemic. Participants completed a survey that included a sociodemographic information form, the State and Trait Anxiety Inventory (STAI), and the Beck Hopelessness Scale (BHS). A total of 135 personnel without a history of psychiatric illness or use of psychiatric medication were included in the study.

Results: Of the 135 participants in the study, 67 were female, and 68 were male. The mean state anxiety score for all participants was 44.5 (12.6), trait anxiety score was 44.2 (7.3) and hopelessness score was 7.1 (5.2). It was found that the anxiety of emergency service workers during the pandemic was at a moderate level and their hopelessness was at a mild level.

In the study, higher scores were found in hopelessness and state-trait anxiety measurements in married individuals compared to single participants (P=0.040, P=0.003, P=0.001, respectively). Trait anxiety scores were significantly higher among those with chronic diseases compared to those without chronic diseases, and in those living with families compared to those living alone (P=0.039 and P=0.017, respectively). A positive and moderate relationship was observed between hopelessness levels and state-trait anxiety levels (P<0.001 for all, r=0.457, r=0.425, respectively).

Conclusion: During the COVID-19 pandemic, increased levels of anxiety and hopelessness were detected among healthcare workers in emergency services. It was observed that as the working time in the emergency department increased, hopelessness and state anxiety levels of the employees also increased.

Keywords: COVID-19, emergency service workers, anxiety, hopelessness

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Introduction

The COVID-19 outbreak originated in China and subsequently swept across the globe, triggering a significant pandemic. The pandemic fundamentally altered the lives of societies socially, economically, and psychologically. It led to approximately 7 million deaths to date. Healthcare workers also experienced high rates of infection and mortality related to the coronavirus. Indeed, healthcare workers on the front line during the pandemic faced numerous challenges and sources of distress. In addition to the high risk of contracting the disease due to their work in intense and stressful environments, healthcare workers also faced other difficulties including transmission of the disease to their families, being separated from their daily lives, feelings of loneliness, and dealing with uncertainties. These additional factors contributed to the overall burden and psychological impact to their well-being [1,2].

Emergency services are dynamic healthcare units where life-saving treatments are provided for sudden situations, such as diseases, accidents and trauma, and where crisis situations are often experienced, and as such, they served as the units where virus-infected patients first applied and initial intervention was performed during the COVID-19 process. The pandemic also generated a number of concerns and worries in people, especially those in high-risk groups. They experienced heightened levels of anxiety as they followed the reported number of cases and deaths in their countries and worldwide and contemplated the risk of contracting the virus and losing their lives [3]. The increased workload and intense work pace during the pandemic, feelings of fatigue and burnout, and concerns about contracting the infection and spreading it to their families were traumatic experiences they underwent. In addition, uncertainty also contributed to increased levels of anxiety among healthcare workers.

Anxiety is a complex emotional state that arises when individuals perceive internal or external circumstances as threatening or endangering to their well-being and overall existence. It may be associated with danger or when a situation is perceived as unsafe [4]. Anxiety is expressed through terms such as worry, distress, overwhelmed, and boredom. According to Spielberger's definition, anxiety is a state involving unpleasant emotional and observable reactions that occur in relation to stressful situations. These reactions may manifest as symptoms, such as sadness, tension, and changes in perception [5]. As a result of his research, Spielberger put forward the concepts "state" and "trait" anxiety and formed the basis of the two-factor anxiety theory [6]. State anxiety refers to a transient and brief experience that is linked to a specific circumstance or occurrence. It arises depending on the current situation or event and usually decreases with the end of the situation. Trait anxiety, on the other hand, refers to a permanent and continuous state of anxiety experienced by individuals in general. Trait anxiety can be associated with factors, such as an individual's personality structure, genetic factors, or childhood experiences, and can be widely felt in daily life without a specific trigger.

Hopelessness is generally defined as having negative expectations about the future [7]. While hope entails the belief that thoughts can be put into action to achieve a goal, hopelessness involves the belief that those thoughts will not come to fruition [8]. Hopelessness consists of emotional, cognitive, and motivational components characterized by negative expectations about the future [9]. It is closely intertwined with an individual's cognitive structure and information processing, serving as a risk factor for anxiety [10]. Hopelessness often leads to negative thoughts about the future, a belief that negative events will occur, and a sense of inadequate coping skills, which can increase anxiety. Similarly, individuals with anxiety disorders may develop a negative perspective about the future, and this may lead to feelings of hopelessness. In the literature, there are studies showing a strong relationship between hopelessness and state-trait anxiety [11,12]. It has been reported that hopelessness, which predisposed individuals to depression and suicidal ideation during the COVID-19 period, was also a positive predictor of COVID-19-related fear [13]. The aim of this study was to evaluate the anxiety and hopelessness levels of frontline emergency service workers in a pandemic hospital during the COVID-19 pandemic in Turkey and to evaluate these parameters in terms of specific variables that may be related to these parameters.

Materials and methods

This cross-sectional study included a sample of 135 emergency service healthcare workers, including doctors, nurses, and healthcare officers, working in Amasya University Sabuncuoglu Şerefeddin Training and Research Hospital from July 10 to August 10, 2020. The researchers enrolled emergency service workers into the study after providing them with comprehensive information about the research and obtaining their signed informed consent. Those who declined to participate and individuals with a history of psychiatric illness or use of psychiatric medications were excluded from the study.

Sample size and power analysis were performed using G*Power 3.1 software. According to G power analysis, the power of the study with 135 participants at 0.52 effect size was found to be 0.82 (power alpha=0.05). Ethical approval for the study was obtained from the Amasya University Non- Invasive Clinical Researches Ethics Committee (Decision No: 2020/43). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments. Participants were administered a sociodemographic information form, the State-Trait Anxiety Inventory (STAI), and the Beck Hopelessness Scale (BHS).

Data Collection Tools

Sociodemographic Information Form: This form included questions regarding the participants' age, gender, marital status, duration of time in emergency services, whether or not they live alone, and if they have any chronic illnesses.

State-Trait Anxiety Inventory (STAI): This assessment was developed based on Spielberger's two-factor theory of anxiety, and it consists of two separate scales comprising a total of 40 items [14]. STAI-1 measures state or situational anxiety level, while STAI-2 measures trait or general anxiety level. Öner and Le Compte [15] have conducted research to establish the validity and reliability of the scale in the Turkish context. Both scales include items with direct and reversed statements. When calculating the results, the total scores obtained from these statements separately are calculated, and the

total score of the reversed statements is subtracted from the total score of the direct statements. A fixed and unchanging value is added to the obtained number to calculate the individual's anxiety score. The values of 50 for STAI-1 and 35 for STAI-2 are used as fixed and unchanging values. Higher scores on the scale are interpreted as higher levels of anxiety. The commonly accepted cut-off score for STAI-1 and STAI-2 is 40. Scores between 0-19 indicate no anxiety; scores between 20-39 indicate mild anxiety; scores between 40-59 indicate moderate anxiety; and scores of 60 and above indicate severe anxiety [16].

Beck Hopelessness Scale (BHS): This scale, developed by Beck et al. [9], is widely used to measure and assess the feeling of hopelessness. Durak and Palabıyıkoğlu [17] conducted the validity and reliability study of the 20-item scale specifically in the Turkish population. According to the scores obtained from the scale, individuals with scores between 4 and 8 are considered to have mild hopelessness symptoms; those with scores between 9-14 have moderate hopelessness symptoms; and those with scores of 15 and above indicate severe hopelessness symptoms [18]. A high score on the scale indicates a heightened degree of hopelessness.

Statistical analysis

The data analysis was performed using IBM SPSS Statistics version 23. To assess normal distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests were employed. For variables that exhibited normal distribution, independent samples t-tests were conducted for comparisons. In cases where variables did not follow a normal distribution, the Mann-Whitney U test was utilized. The relationship between variables was examined through Spearman's correlation analysis. Descriptive statistics such as mean (standard deviation), frequency (n), and percentage (%) were used to present the data. The statistical significance level was set at *P*-value <0.05.

Results

The mean age of the emergency service healthcare workers included in the study was 34.9 (9.0) years, and the mean duration of work in the emergency service was 78.8 (68.9) months. Of the participants, 49.6% were female, 50.4% were male, and 62.2% were married. It was found that 83.7% of the participants did not have any chronic illnesses, and 77.8% lived with their families. Among the 135 emergency service workers, it was determined that 86 (63.7%) had mild levels of hopelessness, 34 (25.2%) had moderate levels, and 15 (11.1%) had severe levels. It was further observed that 49 (36.3%) of the emergency service workers experienced moderate or higher levels of hopelessness. The examination of general hopelessness level and subscale scores among emergency service workers revealed a mean total hopelessness score of 7.1 (5.2). Regarding the subdimensions of hopelessness, the motivation loss subscale had the highest mean score 3.0 (2.2), followed by the subscales of hope 2.5 (2.1), expectations, and feelings about the future 1.6 (1.7). The mean hopelessness score for emergency service workers was found to be 7.1 out of 20, and according to this result, their feelings of hopelessness toward the future was at a mild level. The participants had a mean score of 44.5 (12.6) for STAI-1 and 44.2 (7.3) for STAI-2, concluding that the participants' state and trait anxieties were at a moderate level. Sociodemographic characteristics, findings related to some variables, hopelessness levels, and the analysis findings regarding the mean scores of hopelessness and state-trait anxiety for participants are presented in Table 1.

Table 1: Sociodemographic characteristics, hopelessness levels and descriptive statistics scale scores of participants

	n	%	mean (SD)
Age			34.9 (9.0)
Duration of working in the emergency service (months)			78.8 (68.9)
Gender			
Female	67	49.6	
Male	68	50.4	
Marital status			
Married	84	62.2	
Single	51	37.8	
Chronic illness status			
Yes	22	16.3	
No	113	83.7	
Living alone status			
Alone	30	22.2	
Family	105	77.8	
Hopelessness level			
Mild (0-8)	86	63.7	
Moderate (9-14)	34	25.2	
Severe (15 and above)	15	11.1	
BHS Total			7.1 (5.2)
Expectations and feelings about future			1.6 (1.7)
Motivation loss			3.0 (2.2)
Hope			2.5 (2.1)
STAI-1			44.5 (12.6)
STAI-2			44.2 (7.3)

SD: Standard deviation, BHS: Beck Hopelessness Scale, STAI-1: State-Trait Anxiety Inventory -1, STAI-2: State-Trait Anxiety Inventory-2

When the scale scores of emergency service workers participating in the study were evaluated according to certain sociodemographic characteristics, it was observed that the mean hopelessness score of female healthcare workers 6.1 (4.7) was lower than that of male healthcare workers; however, this difference was not statistically significant (*P*=0.063). The results indicated that gender did not play a significant role in determining the level of hopelessness among emergency service workers. The total score of the Beck Hopelessness Scale (BHS) showed a difference according to marital status (*P*=0.040). The mean BHS score for married individuals was 7.8 (5.3), while it was 5.9 (4.8) for singles. There was no significant difference observed in the total BHS score across other variables (*P*>0.05 for all). The score for expectations and feelings about the future did not show a difference according in the variables (*P*>0.05 for all). The mean motivation loss subscale score for females was 2.4 (2.2), while it was 3.5 (2.1) for males, but this score did not show a difference according to other variables (*P*>0.05 for all). The score for hope did not differ according to the variables (*P*>0.05 for all). When the anxiety scores were analyzed according to variables, the STAI-1 score differed according to marital status (*P*=0.003). The mean STAI-1 value for married individuals was 46.9 (12.0), while it was 40.5 (12.6) for singles. The score for STAI-2 also showed a difference according to marital status (*P*=0.001). The mean STAI-2 score for married individuals was 45.9 (7.0), while it was 41.5 (7.0) for singles. The STAI-2 score was 47.8 (7.6) for those with chronic illness and 43.5 (7.1) for those without chronic illness. The STAI-2 score for individuals living alone was 41.5 (6.2), while it was 45.0 (7.4) for those living with family. The comparisons regarding hopelessness and state-trait anxiety scores of participants according to specific variables are presented in Table 2.

Table 2: The mean scores of BHS and its subscales and STAI-1,STAI-2 according to sociodemographic characteristics of participants

	BHS Total	Expectations and feelings about future	Motivation loss	Hope	STAI-1	STAI-2
	mean(SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Gender						
Female	6.1 (4.7)	1.4 (1.6)	2.4 (2.2)	2.3 (1.9)	45.5 (11.9)	44.4 (6.7)
Male	8.0 (5.5)	1.8 (1.8)	3.5 (2.1)	2.6 (2.3)	43.5 (13.3)	44.1 (7.9)
***P*-value**	0.063	0.227	0.002	0.449	0.360	0.492
Marital status						
Married	7.8 (5.3)	1.8 (1.7)	3.3 (2.3)	2.7 (2.1)	46.9 (12.0)	45.9 (7.0)
Single	5.9 (4.8)	1.3 (1.6)	2.6 (1.9)	2.0 (2.1)	40.5 (12.6)	41.5 (7.0)
***P*-value**	0.040	0.130	0.117	0.058	0.003	0.001
Chronic illness status						
Yes	8.6 (5.5)	2.1 (1.9)	3.5 (2.3)	3.0 (2.0)	45.5 (12.3)	47.8 (7.6)
No	6.8 (5.1)	1.5 (1.6)	2.9 (2.2)	2.3 (2.1)	44.3 (12.7)	43.5 (7.1)
***P*-value**	0.148	0.241	0.307	0.683	0.664	0.039
Living alone status						
Alone	6.4 (4.8)	1.4 (1.6)	2.8 (2.0)	2.2 (2.1)	44.1 (13.0)	41.5 (6.2)
Family	7.3 (5.3)	1.7 (1.7)	3.0 (2.3)	2.5 (2.1)	44.6 (12.5)	45.0 (7.4)
***P*-value**	0.453	0.365	0.789	0.425	0.886	0.017

SD: Standard deviation, BHS: Beck Hopelessness Scale, STAI-1: State-Trait Anxiety Inventory -1, STAI-2: State-Trait Anxiety Inventory-2

A weak positive significant relation was found between work duration in emergency services and the total score on the BHS, motivation loss subscale, hope subscale, and STAI-1 among emergency service healthcare workers (P<0.05 for all) (Table 3). When the relationship between the BHS and STAI-1 and STAI-2 mean scores of the emergency service workers was examined, a noteworthy positive correlation was identified between both state and trait anxiety l levels and feelings of hopelessness among emergency service workers (r=0.457, P<0.001; r=0.425, P<0.001, respectively) (Table 4).

Table 3: The relationship between working duration in the emergency service and scale scores

	Duration of working in the emergency service (months)	
	r	***P*-value**
BHS Total	0.194	0.025
Expectations and feelings about future	0.067	0.443
Motivation loss	0.228	0.008
Hope	0.171	0.047
STAI-1	0.172	0.046
STAI-2	0.051	0.560

r: correlation coefficient, BHS: Beck Hopelessness Scale, STAI-1: State-Trait Anxiety Inventory -1, STAI-2: State-Trait Anxiety Inventory-2, r: Spearman's correlation coefficient

Table 4: The relationship between BHS and STAI-1, STAI-2 scale scores

	BHS Total	
	r	***P*-value**
STAI-1	0.457	<0.001
STAI-2	0.425	<0.001

r: correlation coefficient, BHS: Beck Hopelessness Scale, STAI-1: State-Trait Anxiety Inventory -1, STAI-2: State-Trait Anxiety Inventory-2, r: Spearman's correlation coefficient

Discussion

The COVID-19 pandemic has had significant negative effects not only on individuals' physical health but also on their mental health. Although all individuals were affected by the outbreak, healthcare workers who undertook the treatment and care of patients infected with the virus were more at risk [19]. Emergency services are the units that initially receive patients and provide the first medical interventions, and the healthcare professionals working in these units were at the forefront of the fight during the pandemic. This study aimed to investigate the levels of anxiety and hopelessness among healthcare workers actively serving in the emergency service of a pandemic hospital in Turkey during the COVID-19 pandemic. Additionally, several variables believed to be associated with these levels were examined. The findings were thoroughly discussed in relation to the existing literature.

In our study, we observed that emergency service workers had a mean score of 44.5 for state anxiety and a mean score of 44.2 for trait anxiety. It has been reported that scores of 40 and above on the State-Trait Anxiety Inventory indicate a moderate level of anxiety [16]. Studies have shown that anxiety levels among healthcare workers during the pandemic were higher compared to non-healthcare employees [20]. Factors such as patient workload, direct contact with infected patients, the need to maintain distance from family and relatives, fear of transmitting the disease, and uncertainty may have contributed to increased anxiety levels among emergency service workers.

Results of the present study show that female emergency service workers had slightly higher scores in both state and trait anxiety compared to males, although the observed difference did not reach statistical significance. These findings align with previous studies that indicate women tend to exhibit higher levels of state and/or trait anxiety compared to men [21-23]. The lack of disparity in state and/or trait anxiety between men and women may be attributed to various factors, including life experiences, social and cultural influences, genetic factors, and individual variations. In the analysis of anxiety levels among emergency service workers in relation to their marital status, it was observed that married individuals demonstrated significantly higher state anxiety scores compared to single individuals. Additionally, married individuals exhibited significantly higher trait anxiety scores compared to their single counterparts. This finding is supported by previous studies, however, some studies found higher anxiety levels among singles [21,22]. Factors such as increased shared responsibilities in marriage during the pandemic, limited physical proximity and emotional support due to measures restricting physical contact, increased domestic tensions due to spending more time together at home, and concerns about the future regarding spouses and children could contribute to higher anxiety levels among married individuals.

The analysis of anxiety levels based on the presence or absence of chronic illness revealed a noteworthy finding: Emergency service workers with chronic illnesses exhibited significantly higher levels of trait anxiety compared to those without chronic illnesses. In the study conducted by Karasu et al. [21], it was observed that individuals with chronic illnesses had significantly higher levels of both state and trait anxiety. Similarly, there were studies during the COVID-19 pandemic that reported increased anxiety among healthcare workers with a perception of poor health status; however, other studies suggested no association between anxiety levels of healthcare workers and having a chronic illness [22,24-26]. Factors such as concerns about resistance and immunity to diseases, being in a higher-risk group, increased worries about contracting the virus more easily, experiencing more social isolation than others, and difficulties in accessing healthcare and treatment services could explain the increased anxiety levels in individuals with chronic illnesses.

In terms of anxiety according to whether or not the employee lived alone, it was found that emergency service workers living with families had significantly higher levels of trait anxiety compared to those living alone. Bayülgen et al. [26]

reported that there was no significant difference in coronavirus anxiety levels between individuals living alone and those living with their families. However, Karasu et al. [21] found higher levels of both state and trait anxiety in healthcare workers with children. The elevated anxiety levels observed in married individuals and those living with their families may be attributed to various factors, including concerns about the risk of transmitting the disease to their loved ones, prolonged periods of close proximity at home, fear of potential job loss leading to economic difficulties, and the challenges of maintaining a balance between work and family responsibilities.

In this study, although the general level of hopelessness among emergency service workers during the pandemic was mild, it was determined that some individuals experienced high levels of hopelessness. Among the participants in the present study, 36.3% reported experiencing moderate to high levels of hopelessness. It was determined that the hopelessness levels of emergency service workers during the pandemic did not differ according to gender, chronic illness status, or whether or not they lived alone, but differed according to marital status.

Studies examining the impact of gender on hopelessness levels are consistent with our findings, showing no significant differences in hopelessness levels between men and women [18,23,26]. In our study, we observed that the subscale for motivation loss was significantly higher in men compared to women. These findings align with the results reported in the study conducted by Oğuztürk et al. [27]. However, Ottekin [28] found no significant differences in the scores of hopelessness subscales (hope, motivation loss, expectations and feelings about the future) based on gender in a study conducted with university students. Synder et al. [29], in their study, observed that the gender of students had an impact on the level of hopelessness. In Turkish society, it is believed that upbringing differences, assigned social roles, stress, emotional burden, and hormonal changes between men and women may be determinants of hopelessness levels. The higher scores in the motivation loss subscale among men in our study could be explained by men having difficulty expressing their emotional struggles or a lack of willingness to seek emotional support due to societal norms.

In our study, we observed a significant difference in the levels of hopelessness between married individuals and singles, with married individuals displaying higher levels of hopelessness. Akçöltekin et al.'s [30] study reported significantly higher levels of hopelessness among single students compared to married ones. Researchers have posited that the underlying reason for this finding may be attributed to higher levels of anxiety associated with the prospect of marriage among single individuals. Similarly, there are study findings indicating no significant difference in levels of hopelessness between married and single nurses during the COVID-19 pandemic [26]. These findings are inconsistent with our study. The reason behind this result could be that married individuals may experience higher levels of hopelessness due to being away from their homes, fear of transmitting the disease, limited social interaction, and communication problems during the pandemic.

Another finding of the study was the relationship between the work duration in emergency services and the participants' general level of hopelessness, loss of motivation, and state anxiety. This relationship can be explained by the intense and stressful working conditions in emergency services, exposure to traumatic experiences, time pressure, and irregular working hours such as night shifts.

The identification of a positive and statistical relationship between anxiety and hopelessness levels constitutes another significant finding of our study. There are studies in the literature that support our findings [20,26]. The rapid global spread of the disease, the alarming number of deaths, media portrayal of distressing images, the absence of a definitive treatment, the risk of rapid transmission, and the experience of social isolation during the pandemic can be considered factors that contributed to feelings of hopelessness. Previous studies have consistently demonstrated a strong association between hopelessness and state-trait anxiety [11,12]. Hopelessness and anxiety are intertwined processes. In situations such as a pandemic, the sense of uncertainty and loss of control over the future, negative thoughts regarding what lies ahead, a decline in motivation, and a decrease in overall functioning are believed to collectively contribute to elevated levels of hopelessness and anxiety.

Limitations

This study has several limitations. Firstly, it was conducted in a single center. The sample selected in the study reflects only the emergency department of one pandemic hospital. Secondly, the sample size was relatively small. The changes in the working conditions of emergency service workers during COVID-19 made it difficult to reach a sufficient number of participants. Additionally, the study focused on specific variables influencing hopelessness and anxiety, potentially excluding other important factors that could contribute to a comprehensive understanding of these psychological states. Variables, such as the economic status of the participants, news and media follow-up, loss of relatives or loved ones due to the virus, and whether participants had children may have also affected their anxiety and hopelessness levels during the pandemic, and these variables were not evaluated. Furthermore, the study was conducted with self-report scales completed by the participants. This may have caused biases in the results due to increased workload and working conditions. Statistical analyses may have been affected due to these issues beyond our control. Therefore, studies with larger sample groups and those that evaluate more variables that may affect anxiety and hopelessness should be conducted in healthcare personnel working on the front line in overworked and stressful environments.

Conclusion

In conclusion, this study revealed moderate anxiety and mild hopelessness levels among frontline healthcare workers in the emergency department during the COVID-19 pandemic. The fact that emergency department workers worked under higher risk and difficult conditions compared to other members of the society, changes in the work processes, and adaptation difficulties may have also contributed to increased levels of anxiety and hopelessness. Therefore, it is important to focus on training and informing healthcare workers, improving working conditions, psychological support, regular assessment of mental health symptoms, regular individual sessions, and providing necessary treatment when needed during periods of uncertainty,

trauma, and difficulties such as infectious disease outbreaks. Encouraging healthcare workers to adopt healthy habits such as proper nutrition, regular sleep, stress management techniques, regular exercise, and self-care can also be beneficial in reducing levels of hopelessness and anxiety. This study sheds light on the protection and support of the mental health of healthcare professionals, especially those working on the front line during pandemics.

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Laparoscopic management of an adult abdominal cystic lymphangioma presenting as a retroperitoneal mass with sepsis

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Abstract

Abdominal cystic lymphangiomas are rare entities that can manifest as retroperitoneal cystic lesions, presenting a diagnostic and therapeutic challenge. Managing these cases often requires laparotomy, laparoscopy, or percutaneous intervention, with outcomes varying in terms of success. Here, we present a case of an infected abdominal cystic lymphangioma that was successfully managed through laparoscopy, following thorough preoperative planning.

Keywords: retroperitoneal cyst, abdominal lymphangioma, laparoscopy

Introduction

The retroperitoneal space is an anatomical area between the posterior parietal peritoneum and the posterior abdominal wall. Surgeons face diagnostic and therapeutic challenges when dealing with retroperitoneal masses. While many retroperitoneal masses (RPMs) originate from a specific organ within the retroperitoneum, the exact organ of origin may sometimes be difficult to ascertain. Primary RPMs, on the other hand, do not stem from a specific retroperitoneal organ. They can be classified as either solid or cystic lesions. Primary retroperitoneal neoplasms are extremely rare, accounting for only 0.1–0.2% of all malignancies [1].

This case report presents a rare occurrence of an infected abdominal cystic lymphangioma manifesting as a RPM accompanied by sepsis. The patient was successfully treated using a laparoscopic approach.

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

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Case presentation

A 52-year-old female presented with a 6-month history of abdominal swelling accompanied by diffuse abdominal pain. The swelling had rapidly increased in size over the past 2 weeks and was accompanied by fever.

The patient exhibited a pulse rate of 110 beats per minute during the examination. A diffuse swelling was observed, encompassing the epigastric, left hypochondriac, and umbilical regions. A complete hemogram revealed an elevated leukocyte count of 18,000/µL, while the remaining blood parameters were within normal ranges.

An abdominal MRI was performed, revealing a retroperitoneal cystic mass (Figure 1A) located close to the Aorta and causing compression of the Left Renal vein and Left Ureter, leading to left hydroureteronephrosis. The posterior wall of the cyst was closely adhered to the Aorta, Left renal vein, and lumbar veins (Figure 1B). The cyst wall measured 0.66 cm in thickness and exhibited enhancement, although there was no evident extension to adjacent organs or signs of malignancy.

The patient received IV fluids for resuscitation and was initiated on broad-spectrum IV antibiotics, analgesics, and supportive care. Bilateral DJ stenting was performed, followed by laparoscopy. The laparoscopic examination revealed a large cystic swelling (Figure 2) close to the mesentery of the transverse colon, splenic flexure, and descending colon. Dense omental adhesions were noted along the anterior and lateral walls of the cyst. A 5-mm trocar was used to puncture the cyst, and approximately 700 ml of purulent content was aspirated and sent for culture. Harmonic shears were employed to release the omental attachments, and the splenic flexure and descending colon were mobilized by dividing the gastrocolic ligament. The thick-walled cyst was marsupialized, and the cyst itself was excised, while the posterior wall, which was adherent to the Aorta, left renal vein, and lumbar veins, was left in place.

Figure 1: A: MRI showing the thick-walled cyst(*) measuring 10.9 x 12.6 cm displacing the Aorta (red arrow) to the right, B: Axial section showing the posterior wall of the cyst (*) which is intimately adherent to the lumbar veins (blue arrow) and displacing the Aorta (red arrow)

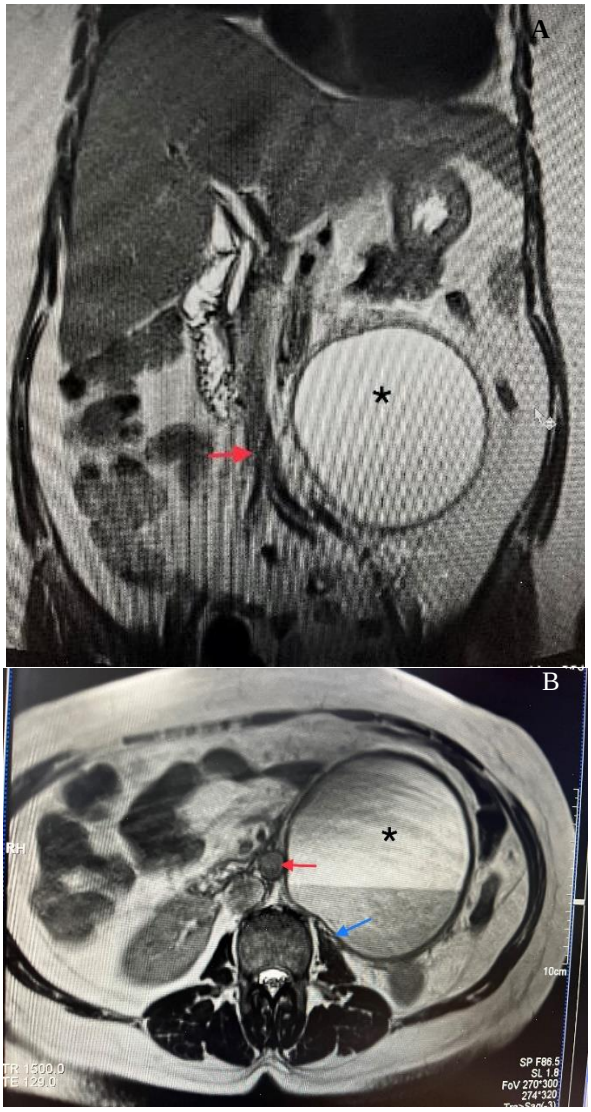
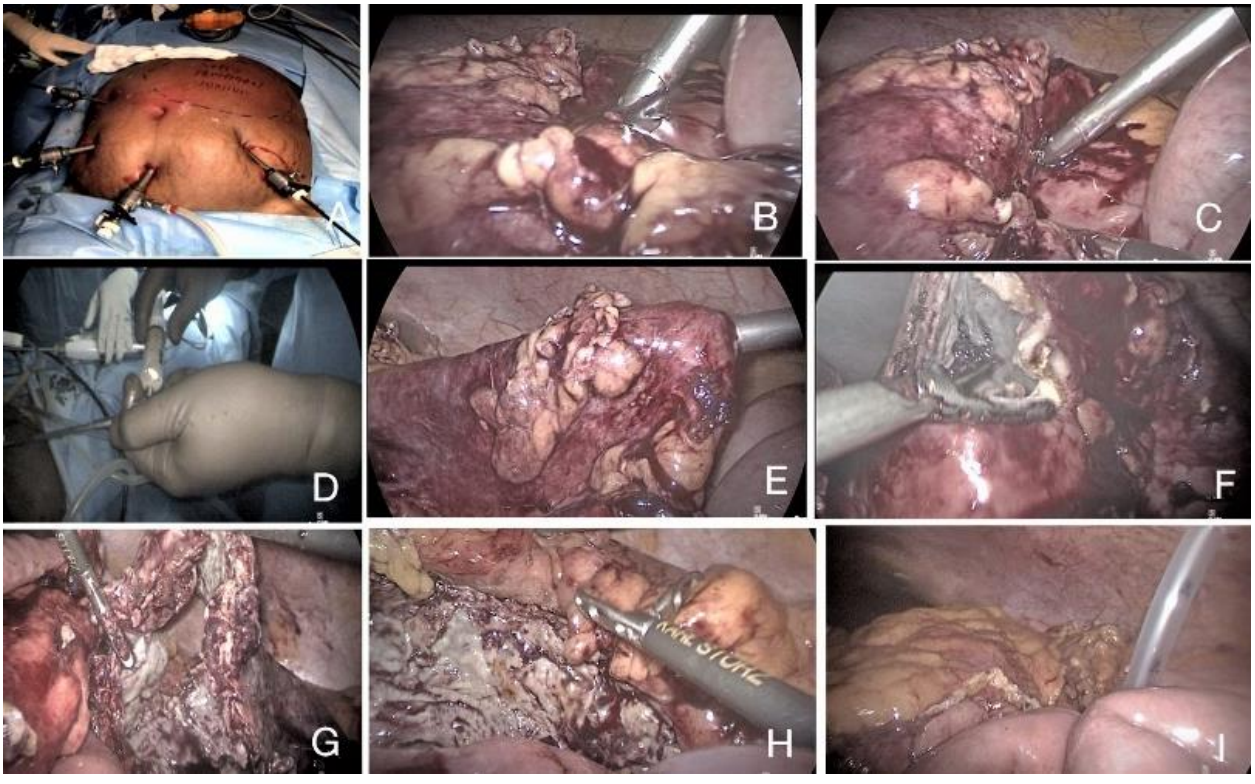
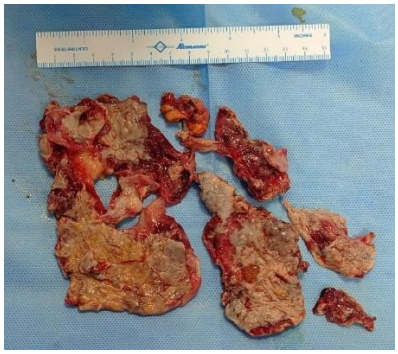


Figure 2: A: Port positions, B: Trocar entry into the cyst cavity, C: Aspiration of contents using suction cannula, D: Sample taken using syringe for culture & sensitivity, E: Complete aspiration of cyst contents, F: Marsupialization of cyst wall using Harmonic shears, G: Exposed cyst cavity, H: View after Complete marsupialization, I: Placement of Drain in the cyst cavity



The specimen (Figure 3) was extracted using an endobag, necessitating the upsizing of the 5-mm port to a 10-mm port. Following the achievement of complete hemostasis, a drain was inserted into the abscess cavity, and the ports were closed.

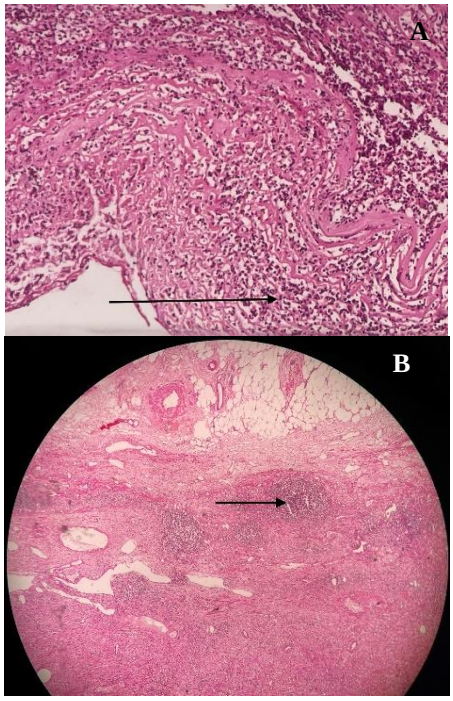
Figure 3: Specimen which was extracted via the 10mm port



The patient's postoperative course was uncomplicated. On the first postoperative day (POD), the patient experienced postoperative ileus, but oral feeds were gradually introduced and well tolerated thereafter. The patient was discharged on POD5. The abdominal drain was removed on POD8. Pus culture results showed no growth after two days of aerobic incubation.

Histopathological examination revealed a fibrous cyst wall with prominent inflammatory infiltrates (Figure 4A), the presence of foamy macrophages, hemorrhage, and lymphoid aggregates (Figure 4B), without any indications of malignancy. The DJ stents were removed after a period of 4 weeks, and a subsequent 6-month follow-up showed no notable events or complications.

Figure 4: A: Histopathology of showing fibrous cyst wall with dense inflammatory infiltrates (black arrow), B: Sections from the cyst wall showing foamy macrophages, hemorrhage, neutrophilic infiltrates and lymphoid aggregates (black arrow)



Discussion

Lymphangiomas arise from abnormal connections within the lymphatic channels, leading to impaired lymphatic drainage and subsequent cystic dilatations of the lymphatic vessels [2]. Although most documented cases of cystic lymphangiomas are observed in the pediatric population, the clinical presentation and characterization of these lesions in adults remain unclear [3]. While axial and cervical regions are commonly affected by cystic lymphangiomas, abdominal cystic lymphangiomas are considered rare entities. Given the mesentery's dense lymphatic network, it is the preferred location for the development of lymphangiomas.

Typical manifestations of abdominal cystic lymphangiomas often involve abdominal pain and compressive symptoms. In rare cases, these cysts may become infected, leading to the development of sepsis. Infections can occur either as primary infections or secondary infections via hematogenous spread or involvement of adjacent organs [4].

The initial investigation for abdominal lymphangioma typically involves an ultrasonogram, which can detect a cystic mass characterized by anechoic areas but may also exhibit echogenic debris. These cysts can present as multilocular structures with septations or as uniform unilocular cysts. Contrast-enhanced CT scans can enhance the visualization of the cyst wall and septations. MRI, with its high soft tissue resolution and the ability for multiplanar reconstruction, is valuable for preoperative planning, particularly in cases involving large cysts that exert pressure on adjacent structures [5].

Treatment options for abdominal lymphangiomas encompass percutaneous aspiration, laparotomy, and laparoscopic surgery. Percutaneous aspiration and injection of sclerosants have been attempted; however, they are associated with high rates of recurrence [3]. Laparotomy involves making a large incision to access the entire cyst and is linked to morbidity and wound complications.

Complete resection of the cyst may not always be feasible due to its location and close adherence to major vessels and colonic vasculature. In this particular case, the posterior wall of the cyst was intentionally left in place due to its adherence to the abdominal Aorta, left renal vein, and lumbar veins. At the 6-month follow-up, the patient remains asymptomatic.

Conclusion

The laparoscopic management of large retroperitoneal cystic masses is technically feasible, but it necessitates meticulous preoperative planning.

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