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Determination of the Effect of Epigallocatechin Gallate on Oxidative Stress, Apoptosis and Sperm Quality in Rabbit Semen

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Abstract: In this study, it was aimed at determining the effect of Epigallocatechin gallate (EGCG) on the cryopreservation of rabbit semen. In the study, semen was collected from six male New Zealand rabbits using an artificial vagina. Collected semen control was divided into 5 groups as 25 µM, 50 µM, 100 µM and 200 µM. After adding EGCG to the extender, semen samples were frozen and thawed. After freezing and thawing, total motility, progressive motility and the rate of fast and medium speed spermatozoon were found to be statistically high in the 50 µM group. The static sperm ratio was found to be lower in the 50 µM group than in the other groups. When the flow cytometry results were examined, there was no statistical difference between the groups in terms of the ratio of dead and live sperm. However, the rate of dead sperm with acrosome damage was found to be the lowest in the 50 µM group. The high mitochondrial membrane potential sperm ratio was found to be higher in 50 µM and 100 µM groups compared to other groups ($p<0.05$). The apoptosis rate was numerically the lowest in the 25 µM and 50 µM groups. While the rate of ROS was the highest in the control group, it was significantly reduced in all EGCG support groups. In conclusion, the addition of EGCG to the dilution of rabbit semen improved semen quality in a dose-dependent manner. ©2023 NTMS.

Keywords: Antioxidants; Cryopreservation; Epigallocatechin Gallate; Rabbit; Semen.

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1. Introduction

Rabbits are widely used as animal models, as they have a similar lipid metabolism to humans [1]. Therefore, it is important to preserve rabbit genes as a biological resource and semen must be cryopreserved for long-term storage [2]. Since semen can be obtained from rabbits without euthanasia, the method of freezing rabbit semen is frequently used in experimental studies. However, the motility of spermatozoa decreases after freezing and thawing [3]. The rate of decrease in sperm motility after freezing is a major disadvantage for the use of frozen semen [4]. Cryopreservation of rabbit semen causes oxidative stress, decreased motility percentage, and decreased life span of spermatozoa [5]. This has been proven in several animal species and is supported by reduced DNA integrity as well as reduced sperm motility, damaged sperm cell membranes and premature acrosome reactions. [6]. Oxidative stress also causes losses in morphological integrity, and fertilization ability and induces sperm apoptosis [7]. To protect sperm cells against cryo-damage, extenders should be supplemented with cryoprotective and antioxidant substances [8].

The major polyphenolic compound in green tea is epigallocatechin-3-gallate (EGCG) [9]. EGCG is a natural antioxidant that can be used to treat problems related to male infertility, the fertilization rate of oocytes and maturation rate of embryos [10]. EGCG increases endogenous antioxidant activity and eliminates free radicals by reacting with hydrogen, alkoxyl or peroxyl radicals. [11],[12]. Sperm mitochondria are organelles damaged by cryopreservation [13]. EGCG is accumulated in mitochondria and maintains catalase activity [14]. In buffalo semen, 200 µM and 300 µM doses of EGCG were added to the cryo-diluent medium, and it was stated that total motility and progressive motility ratio, rapid velocity value, plasma membrane integrity and function were positively affected [15]. Doses of EGCG have been noted to increase cholesterol efflux and tyrosine phosphorylation through the estrogen receptor in human semen. It has been stated that EGCG increases sperm motility, viability and proteins that control cell viability such as Bcl2, Akt and Src via the ER. In addition, a decrease in triglyceride content, lipase induction as well as a decrease in G6PDH activity were observed [16]. In horses, EGCG at concentrations of 10 µM and 20 µM caused a significant increase in the number of sperm bound to zona pellucida [17, 18]. In pigs, EGCG increased sperm oocyte penetration and the total fertilization rate was found to be high in IVF [19]. In another study, EGCG treated arsenic-induced disruptions in epididymal sperm concentration, structural membrane integrity in kinematic properties, functional membrane integrity, and improved the impaired antioxidant defense system [20].

In the literature review, no experimental study was found that investigated the effect of EGCG on semen cryopreservation in rabbits. Therefore, in this study, the cryopreservative effects of EGCG supplementation in rabbit semen were investigated by CASA parameters. After cryopreservation, the effects on dead sperm ratio, acrosomal damage, reactive oxygen species (ROS) ratio as a marker of oxidative stress, mitochondrial membrane potential and apoptosis were investigated by flow cytometry.

2. Material and Methods

2.1. Animals, semen collection and cryopreservation process

All experimental procedures were carried out under the guidance of the European Union Directives for the Care and Use of Laboratory Animals. Six male New Zealand rabbits were used in the study. Rabbits were housed in standard conditions throughout the study. Animals were given feed and water ad libitum throughout the study. Ejaculate was collected from animals once a week. The gel part was removed from the ejaculate and motility was determined. The ejaculates were diluted 1:1 with Tris egg yolk diluent and pooled. Pooled semen samples were divided into 5 equal volumes by adding EGCG according to the groups to be diluted with 1/1 tris-egg yolk containing 5% DMSO in the final volume. It was diluted with spermatozoa in a final volume of $170x10^6$/mL [17].

Semen samples separated into groups were gradually cooled to 4 °C in approximately 90 minutes [21]. Semen analysis at +4 °C was performed with the computer assisted semen analysis (CASA) system (ISAS 2, Proiser, Spain) [22]. Sperm samples were drawn into straws with a volume of 0.25 mL and frozen with the help of a sperm freezing device (Minidigitcool, IMV, Spain). Frozen semen samples were thawed at 37°C for 30 seconds [23], after 2 months and analyzed [21]. Then, 10 µl of sperm samples were taken from all groups and analyzed by CASA.

2.2. Flow Cytometric Analysis

2.2.1. The Rate of Viable Sperm

The dead-viable sperm ratio was determined by the SYBR-14/PI staining kit [24]. Diluted semen samples were mixed with 2.5 µL of SYBR-14 and 2.5 µL of PI and incubated for 10 minutes at 22°C and analyzed.

2.2.2. Acrosomal Status

It was determined by the FITC-PNA/PI staining method [25]. 860 µL of PBS was placed on 30 µL of semen sample. It was incubated for 15 minutes with 5 µL of PNA and 2.5 µL of PI. The cytometer's 488 nm argon ion laser was used to excite fluorochromes, PI and FICT-PNA.

2.2.3. Sperm Apoptosis Rate

Briefly, 100 µl of the sperm sample was taken and incubated in an eppendorf tube containing 5 µL of annexin V and 5 µL propidium iodide (PI). It was then analyzed by flow cytometry [26].

2.2.4. Mitochondria membrane potential assay
For mitochondrial membrane potential (MMP) spermatozoa percentage, semen samples were washed with phosphate buffer solution (PBS) and analyzed with the commercial JC-1 commercial kit according to the manufacturer's instructions[27].

2.2.5. Reactive Oxygen Species Analysis
Reactive oxygen species analysis was determined using 2,7-dichlorodihydrofluorescein diacetate (H2DCFDA; Invitrogen) and double staining with PI.[28]

2.3. Statistical Analysis
Statistical analyses of the data were performed via the SPSS (Version 26, SPSS, Chicago, IL) program. Values are expressed as Mean±S.E.M. Post hoc Tukey test and one-way ANOVA method were used to determine the differences between the groups.

3. Results

3.1. Sperm analysis results 4 ºC degree
The analysis results for cooled semen samples are presented in Table 1. Accordingly, no statistical difference was found between the experimental groups of EGCG and the control group.

Table 1: Sperm analysis results with CASA at 4 oC degrees after equilibration.

	Control	**25 µM**	**50 µM**	**100 µM**	**200 µM**
Total Motility (%)	59.55±10.74	64.45±5.33	68.58±7.46	66.15±5.51	61.98±6.06
Progressive Motlility (%)	29.18±4.54	39.88±6.95	40.20±10.72	42.78±8.50	40.15±9.41
Rapid (%)	43.78±9.58	50.58±6.52	43.86±21.33	49.30±7.12	48.86±7.70
Medium (%)	8.11±3.79	7.76±4.51	10.6±3.40	7.40±2.36	9.58±3.86
Slow (%)	10.96±9.59	5.66±4.19	3.70±0.96	5.46±3.09	3.21±1.11
Static (%)	37.11±11.86	36.08±5.63	31.58±10.51	34.51±5.18	38.35±5.97
VCL (µm/s)	90.21±15.36	93.83±16.42	92.80±18.67	92.05±7.85	94.91±17.39
VSL (µm/s)	41.93±17.12	41.33±11.67	42.33±14.67	43.56±11.30	45.70±17.95
VAP (µm/s)	56.51±16.82	55.75±13.71	57.21±17.28	56.13±7.14	60.36±19.09
LIN (%)	45.10±11.73	44.76±9.73	45.05±9.35	47.61±17.13	47.43±13.43
STR (%)	72.13±9.36	73.86±9.12	72.76±8.82	76.65±11.90	74.71±12.55
WOB (%)	61.63±8.55	59.30±7.86	60.90±7.80	61.08±6.76	61.71±9.68
ALH (µm)	3.36±0.64	3.28±0.36	3.30±0.64	3.28±0.36	3.25±0.48
BCF (Hz)	8.84±0.78	9.50±0.40	9±0.44	9.58±0.73	9.20±0.60

No statistical difference was found in the data without superscript. VCL=Curvilinear velocity; VSL=Straight linear velocity; VAP=Average path velocity; LIN=Linearity; STR=sperm track straightness; WOB=Wobble; ALH=Amplitude of lateral head displacement; BCF=Beat cross-frequency.

3.2. Sperm analysis results after freezing and thawing
The CASA analysis results for cooled semen are shown in Table 2. Total motility and progressive motility percentage was highest in 50 µM EGCG group (P<0.05). While the highest percentage of rapid spermatozoa was found in the 50 µM group, a statistical difference was found between the control and 200 µM groups (P<0.05). The highest percentage of medium spermatozoa was found in the 50 µM group, while a statistical difference was found between the control group (P<0.05). The static sperm ratio had the lowest value in the 50 µM group (P<0.05).

3.3. Flow cytometry analysis results after freezing and thawing
Flow cytometry analysis results are shown in Table 3. There was no significant difference between the groups in terms of percentage of dead sperm ratio by flow cytometry. However, the lowest rate of acrosome-damaged dead sperm was observed in the 50 µM group. The high mitochondrial membrane potential (HMMP) spermatozoon value was higher in the 50 µM group (P<0.05). While the lowest percentage of apoptosis was seen in the 25 µM and 50 µM groups, there was no statistically significant difference between the groups.

Table 2: Sperm analysis results with CASA after the freezing thawing process.

	Control	25 µM	50 µM	100 µM	200 µM
Total Motility (%)	17.38±3.35^{a*}	22.73±4.68^{a}	31.11±5,46^{b*}	23.61±5.44^{ab}	21.23±2.47^{a}
Progressive Motlility (%)	10.08±0.39^{a}	14.61±3.50^{ab}	19.18±4.48^{b}	14.08±4.80^{ab}	13.60±2.17^{ab}
Rapid (%)	10.35±4.19^{a}	14.31±4.03^{ab}	19.36±3,36^{b}	13.45±2.24^{ab}	12.55±4^{a}
Medium (%)	3.16±2.24^{a*}	5.63±1.00^{abc}	8.03±1.24^{c*}	5.86±1.24^{bc}	4.53±1.77^{ab}
Slow (%)	3.85±3.52	2.78±0.87	4.73±0,93	5.05±3.01	3.23±0.94
Static (%)	82.61±3.35^{b}	77.26±4.68^{b}	67.88±5.25^{a}	76.55±5.52^{b}	78.76±2.47^{b}
VCL (µm/s)	76.83±25.92	74.21±16.70	79.01±13.07	71.01±6.40	67.66±37.53
VSL (µm/s)	38.56±20.51	38.76±12.53	39.51±17.07	37.23±10.42	40.46±13.30
VAP (µm/s)	48.06±23.52	45.40±14.91	48.08±13,62	43.76±10.02	48.35±13.37
LIN (%)	49.05±12.77	51.65±7.81	50.25±17.22	51.91±11.61	51.40±11.91
STR (%)	79.25±8.24	72.86±33,81	80.50±11.76	84.16±5.71	83.31±9.95
WOB (%)	61.13±11.11	60.33±8.26	61.03±12.78	61.16±10.24	61.23±9.39
ALH (µm)	3.01±0.36	2.86±0.33	2.93±0.40	3.15±0.33	3.06±0.30
BCF (Hz)	8.23±1.47	9.05±1.26	8.88±0.83	8.66±0.46	8.71±0.97

Different superscript letters (a, b, c, P < 0.05, *; P<0,001) in the same row display significant differences between the groups. VCL = Curvilinear velocity; VSL = Straight linear velocity; VAP = Average path velocity; LIN = Linearity; STR = sperm track straightness; WOB = Wobble; ALH = Amplitude of lateral head displacement; BCF = Beat cross-frequency.

Table 3: Flow cytometry analysis results in frozen thawed semen.

	Control	25 µM	50 µM	100 µM	200 µM
Rate of dead spermatozoa %	78.75±8.13	79.08±9.89	78.35±5.93	81.38±5.22	84.5±8.45
Rate of dead sperm with acrosomal damage %	32.87±13.30^{ab}	28,83±2.99^{ab}	24.89±6.15^{a}	35.05±4.13^{ab}	39.74±6.67^{b}
Rate of viable sperm with acrosomal damage %	0.33±0.24	0.55±0.31	0.20±0.18	0.39±0.41	0.40±0.31
High mitochondrial membrane potential rate %	20.33±2.72^{a}	19.56±1.55^{a}	26.82±2.89^{b}	26.25±3,53^{b}	20.02±2.70^{a}
Apoptosis %	11.21±3.82	9.53±1.40	9.30±2.02	12.47±2.54	13.44±3.54
ROS ratio %	39.77±10.59^{a*}	15.75±10.83^{b*}	14.63±3.04^{b*}	15.39±2.21^{b*}	14.80±6.27^{b*}

Different superscript letters (a, b: P<0.05, *: P<0,001)in the same row display significant differences between the groups.

4. Discussion

Sperm cryopreservation causes a decrease in viability, motility and MMP, while causing an increas in apoptosis, DNA damage and ROS levels [29]. Rabbits are well suited for biomedical research [30]. After the cryopreservation of rabbit semen, a decrease occurs in rabbit sperm quality [31]. Therefore, in this study, the effects of EGCG supplemention semen extenders in New Zealand rabbits after freeze thawing were investigated.

Sperm quality predicted by CASA is a marker of cryopreservation and fertilization capacity of spermatozoa in animals [32]. Sarıözkan et al.[33] in their study with L-carnitine, stated that sperm motility increased between 0.5 and 2 mM in 12 and 24 hours of storage. However, they could not find a statistical difference between 0 and 6 hours in their study. In a study, three important components of tea (caffeine, EGCG and L-theanine) were stored in rat epididymal sperm at room temperature for 3 days and it was stated that these three compounds were eneficial for sperm storage [34]. While there was no statistical difference between the experimental groups in the cooled semen samples in our study, total and progressive motility values were found to be high in the 50 µM EGCG group after freezing and thawing (P<0.05). For this reason, EGCG was thought to have cryoprotectant properties as well as antioxidant properties. It is reported that 300 µM EGCG added to the cryomedium in buffalo spermatozoa improved CASA parameters [15]. In human semen, 2 to 20 µM EGCG caused an increase in sperm motility [16]. In stallion semen, 10 and 20 µM EGCG caused an increase in sperm motility [18]. In another study, it is stated that 50 µM EGCG increased the total motility and progressive motility values of stallion semen after cryopreservation [35]. In our study, it was observed that sperm motility gradually decreased in rabbits at doses above 50 µM EGCG. It is thought that this situation is caused by the differences in spermatozoon structure and membrane composition of different species.

The major problem in sperm cryopreservation is the ice crystals produced during the freezing process and consequently the reduced viability of the sperm [36]. In our study, there was no statistical difference between the groups in terms of the percentage of dead sperm. The rate of dead with acrosomal damaged sperm was statistically low in the 50 µM group. This suggests that EGCG at a dose of 50 µM can be used as an effective energy source in semen.

Successful preservation of semen in rabbits depends on procedures in sperm cryopreservation [30]. The sperm cryopreservation process, which includes cooling, freezing and thawing, causes damage to the sperm

membrane and genome structures [37]. Sperm cryopreservation increases oxidative stress and decreases antioxidant capacity [38]. Spermatozoa are exposed to oxidative stress during cryopreservation [39], so antioxidant substances should be added to the cryopreservation medium to improve sperm quality [30]. ROS has been tried to be eliminated by adding various antioxidant substances to the cryomedium of rabbit semen [40]. Together with the cellular enzymatic defense system, including CAT, SOD1, SOD2 and GPx, EGCG can enhance the antioxidant defense system of germ cells [41]. It is stated that EGCG may also offer a protective role against cellular oxidative damage involved in the pathogenesis of male infertility [42]. EGCG administration prevents the increase of hydrogen peroxide (H_2O_2) and malondialdehyde (MDA) [43]. Physiological ROS levels drive tyrosine phosphorylation cascades during sperm capacitation [44]. In our study, the rate of ROS was lower in all EGCG supplement groups compared to the control groups. However, a significant increase in total motility and progressive motility values is observed at 50 µM dose ($P<0.05$). Although very small changes were observed in the rate of ROS in a dose-dependent manner, it was interpreted that the effect of EGCG on sperm motility was mostly associated with acrosomal damage and HMMP.

Apoptosis can be induced by oxidative stress due to damage to mitochondria, plasma membrane and core material [45]. Increased oxidative stress in cryopreservation causes apoptosis by damaging the nucleus, acrosome and spermatozoa membrane [46]. ROS-induced oxidative stress is considered as the main cause of apoptosis [47]. Spermatogenesis in the seminiferous epithelium is accompanied by germ cell apoptosis. Apoptosis of germ cells is required to maintain an optimal germ cell ratio and to remove abnormal germ cells [48]. It is stated that exogenous EGCG supplementation can provide protection against short-term germ cell loss through mitogen-activated protein kinase, Bcl2 family and caspase 3 pathway [10]. The apoptosis rate was the lowest in the 50 µM group among the experimental groups without statistical difference. It is thought that the use of agents with antioxidant effect, suppressing oxidative stress and thus inhibiting apoptosis in sperm cryopreservation is important in this respect.

5. Conclusions

This study was conducted to elucidate the possible mechanism of action of EGCG, the major phenolic compound found in green tea, in semen cryomedium in rabbits. In the study, semen cryopreservation was performed using New Zealand rabbits.

The results showed that EGCG dose-dependently increased sperm quality in semen cryomedium, decreased the total ROS ratio significantly at all doses of EGCG, increased the mitochondrial membrane potential, reduced acrosomal damage, and partially affected the apoptosis rate.

Limitations of the Study

None.

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Our study was presented in the summary statement at the CRYO2023 congress (Minneapolis, USA).

Conflict of Interests

The authors declare no competing interests.

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Author Contributions

SAA designed the study. ÇCA, RHK, TCA, İHG and SAA contributed to data collection and data analysis. GT, MS, SG and ADÖ read the draft and approved the final scenario. HEE ensured the project completion.

Ethical Approval

Approval for this study was obtained from the Fırat University Animal Experiments Local Ethics Committee (Protocol No. 2021/14).

Data sharing statement, Consent to participate and Informed Statement

None.

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Radiological Characteristics of Immunization Adenitis in the Axilla Following the Covid-19 Vaccine

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Abstract: It was aimed to investigate the ultrasonography (US) features of axillary COVID-19 immunization adenitis. Patients with axillary COVID-19 immunization adenitis detected between April 2021 and January 2022 were included. US features of the lymph nodes identified at the patient's initial US were all recorded. Radiological follow-up information and if exists pathology results were investigated. 104 immunization adenitis in the axilla following Covid-19 vaccine were detected. Only 18.3 percent had axillary pain or edema. Biopsy was recommended for 4 patients and follow-up was recommended for the other 100 patients. Core biopsy results were lymphoid tissue with focal micro-abscess formations, reactive lymphoid hyperplasia and plasma cell increase. All of the patients had a history of vaccination in the last 3 months. After immunization, initial US imaging was conducted mean 24-days later. The mean long and short axis were 22-mm and 13-mm, respectively. The mean long-short axes ratio was 2.2. The mean thickness of the cortex was 4.8-mm. The long and short axes of the lymph nodes in the first US and control examinations were compared statistically and they decreased in time. The hilum existed (96%). Elastography revealed soft features. The majority of the immunization adenitis are just enlarged benign-appearing lymph nodes. The majority were found during the extensive immunization campaign and were asymptomatic. Patients and their physicians should be aware of the vaccination and imaging evaluation of specific patient groups considering that these vaccinations will continue to be used for a while in the next years. ©2023 NTMS.

Keywords: Axillary Lymph Nodes; Covid-19; Lymphadenopathy; Vaccine.

1. Introduction

Millions of lives are saved annually thanks to vaccination, which is a success story in global health and development. In order to create immunity, vaccines act in conjunction with your body's natural defences. Your immune system reacts when you receive a vaccination [1,2]. Although immunizations are generally regarded as safe, the most frequent side effects are local adverse reactions, such as discomfort, swelling, and redness at the injection site. They often start a few hours after the injection and are usually neither severe or self-limited. Depending on the vaccine type, up to 80% of vaccine doses may cause local responses.[3] It is recognized that some vaccines can cause adenitis [4]. Instead of being an illness, it is the body's response to the vaccine; it is a sign of immunization [5]. Even though many vaccines cause immunization adenitis, the axilla

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is a significant location that warrants attention and caution, especially in some particular groups [6-8]. Actually, the axilla is an intersection. In addition to diseases of the lymph nodes themselves, it accepts lymphatic outflow of the breast, lungs, upper extremities, and the skin that covers these areas [9, 10]. It is therefore essential to determine the source of an abnormal finding in the axilla. In this study, we aim to demonstrate the radiological characteristics of patients with COVID-19 immunization adenitis.

2. Material and Methods

The study received approval from the non-interventional clinical research ethics committee at our university in a decision with the reference number E-10840098-722.02-4333. As a retrospective observational study, informed consent could not have been acquired.

2.1. Patients

Between April 2021 and January 2022 in the Radiology department axilla US findings were reviewed. Patients having COVID-19 immunization adenitis were. Patients who underwent evaluation between these dates and had previously been diagnosed with pathologically benign lymphadenitis or axillary involvement due to breast, lung or head and neck carcinoma were excluded from this study. The dimensions, shapes, thicknesses of the cortex, vascularity, and elastic stiffness of the lymph nodes identified at the patient's initial visit were all recorded using ultrasonography. Radiological follow-up information and if exists pathology results were investigated. Detailed clinical history and vaccination history of each patient were obtained before ultrasonography and recorded. A short wait, 1-month, and 3-month US control were recommended for patients with immunization adenitis.

2.2. Axilla Ultrasonography

As per institutional procedure, ultrasonography was performed by a high-frequency (12 MHz) linear transducer. The axilla was assessed in ultrasonography by comparison on both sides. Atypical lymph nodes were enlarged, round or those with a thickened cortex (greater than 3 mm), a flattened or missing hilum [11]. The patients with the diagnosis of immunization adenitis were advised to undergo follow-up or biopsy if an abnormal lymph node was found in the axilla and there was a history of vaccination given to the same arm during the previous three months.

2.3. Statistical Analysis

The statistical analysis was carried out using SPSS 22.0 software. Counts and percentages were used to report categorical data, whereas the mean and standard deviation were used to display continuous variables. The distribution of the data was confirmed using the one-sample Kolmogorov-Smirnov test. When a normal distribution could not be determined, log transformation was used. Descriptive statistics were employed. The Wilcoxon test was used to assess the short and long axes and long-short axes ratio that was captured in the initial and subsequent US exams. Every analysis was two-sided, and a statistically significant level of significance was set at 0.05.

3. Results

On the specified dates, 1934 superficial tissue US was performed in the Department of Radiology. Axilla assessment was performed in 230 of these. Among them 104 had immunization adenitis in the axilla following Covid-19 vaccine (101 females (97%), 3 males (3%); mean±standard deviation (SD), 37±9 year-old) were involved. Only 19 patients (18.3 percent) of those we questioned in the first US reported experiencing axillary pain or edema. Among those recommended biopsies, 1 patient did not accept the biopsy and did not come to the controls. It was reported as the results of 3 patients who underwent core biopsy were lymphoid tissue with focal micro-abscess formations, reactive lymphoid hyperplasia and plasma cell increase. The months in which the patients were examined initially are given in Figure 1.

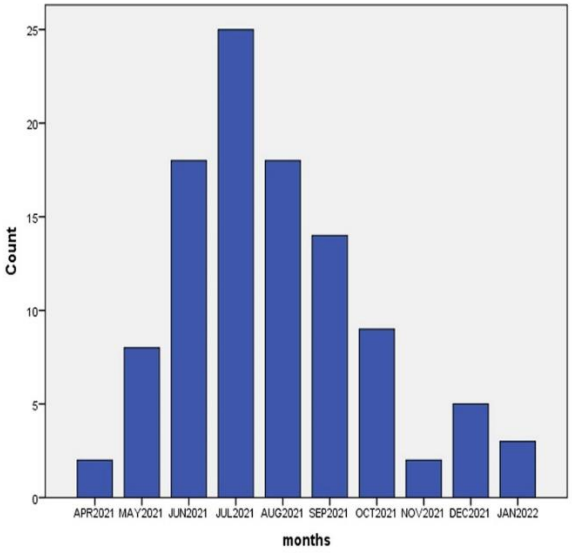

Figure 1: The months in which the patients were detected.

All of the patients had a history of vaccination in the last 3 months. After immunization, US imaging was conducted Mean±SD, 24±29-days later (between 1 and 160-day). Biopsy was recommended for 4 patients and follow-up was recommended for the other 100 patients. After an average of 90±56 days (15-212), 31 of them came to the first control and 10 of them came to the second control after an average of 191±31 days (137-225). 51 patients were called and invited to the US for control, but they chose not to come because they had no complaints.

The lymph node was located on the left in 87 patients (84%), bilateral in 14 patients (13.5%), and on the right in 3 patients (2.5%). In 90 patients, the lymph node arose on the same side as the vaccinated arm (86.5%), while it appeared bilaterally in 14 patients (13.5%).

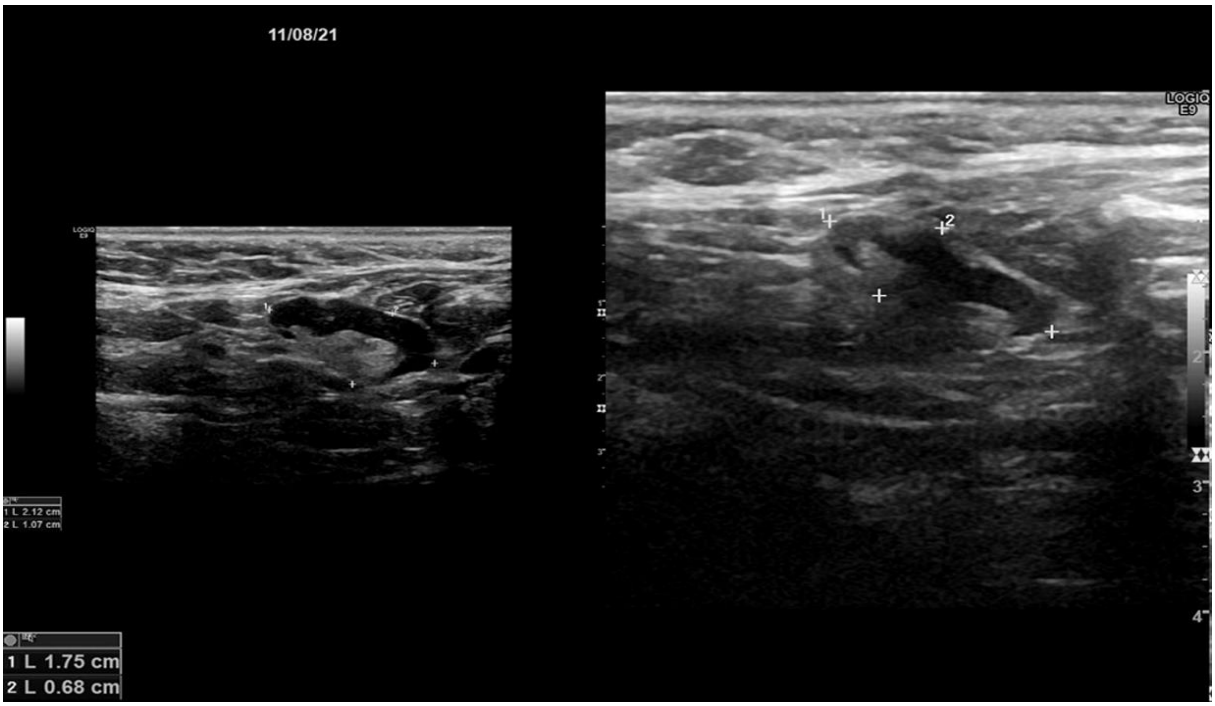

Figure 5: An oval, thick cortex, enlarged lymph node is observed in a 37-year-old female patient who was vaccinated against COVID-19 (left). In the first US control, it is noteworthy that its size has decreased, its cortex has become thinner and its hilum has become prominent (right).

Table 1: The dimensions of the lymph nodes in the first US and control examinations.

	Long Axis (Mean±SD)	**Short Axis (Mean±SD)**	**Long-Short Axes Ratio (Mean±SD)**
Initial US	22±6 mm	13±11 mm	2.2±0.6
First control	18±3 mm	10±4 mm	2.4±0.7
Second control	17±3 mm	9±4 mm	2.6±1.3
Comparison of the initial US and the first control (p value)	0.004*	0.045*	0.012*
Comparison of the initial US and the second control (p value)	0.010*	0.077	0.210
Comparison of the first and the second controls (p value)	0.223	0.069	0.184

The Wilcoxon test was used. *Statistically significant.

In the initial ultrasonography, the mean long and short axis of the lymph nodes were 22±6-mm (8-49) and 13±11-mm (4-58) respectively. The mean long-short axes ratio was 2,2±0.6 (0.3-4.0). 100 (96%) of the lymph nodes were oval and 4 (4%) round. The mean thickness of the cortex and SD was 4.8±1.9-mm (2-13.8 mm). The long and short axes of the lymph nodes in the first US and control examinations were compared statistically and significant difference existed between the initial US and the others (Table 1, Figures 2-5).

The hilum was missing or flattened in 4 lymph nodes (4%), while in others do exist (96%). While the expression of hilar blood supply for 18 lymph nodes was included in the report, the anarchic blood supply was not mentioned in any of them. Elastography information was available for only 20 lymph nodes. Elastography revealed soft features in 19 lymph nodes (95%), and a stiff elastic score for only one lymph node (5%). All but one patient had received the mRNA vaccine.

4. Discussion

The majority of the lymph nodes in our study population with COVID-19 immunization adenitis are oval-shaped, benign-appearing, have a distinct hilum, normal hilar vascularity, are soft on elastography, with normal long-short axes ratio, and only have increased dimensions. 99 percent of cases were due to mRNA vaccination. The bulk was found during the extensive immunization campaign that took place between June and October of 2021 and was asymptomatic.

An oval or lobulated shape, as well as a smooth, clearly defined edge, are characteristics of a healthy axillary lymph node. The cortex should be uniformly thin, measuring 3 mm or less, and mildly hypoechoic [12].

Normal, non-metastatic lymph nodes have long-short axes ratio greater than 1.6 [13].

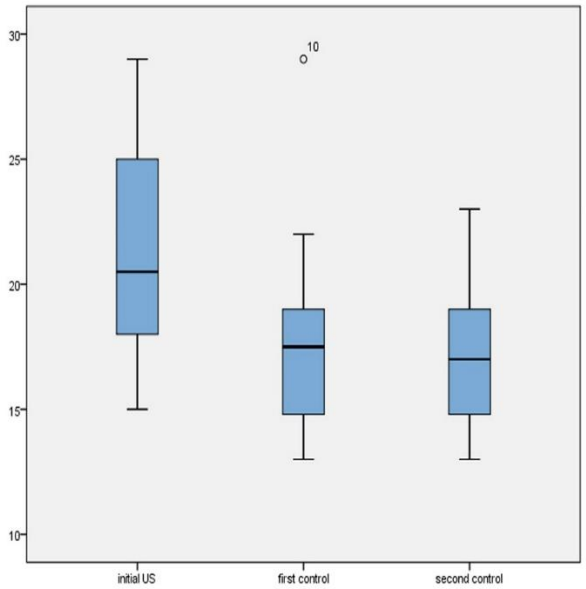

Figure 2: The long axis of the lymph nodes in the first US and control examinations.

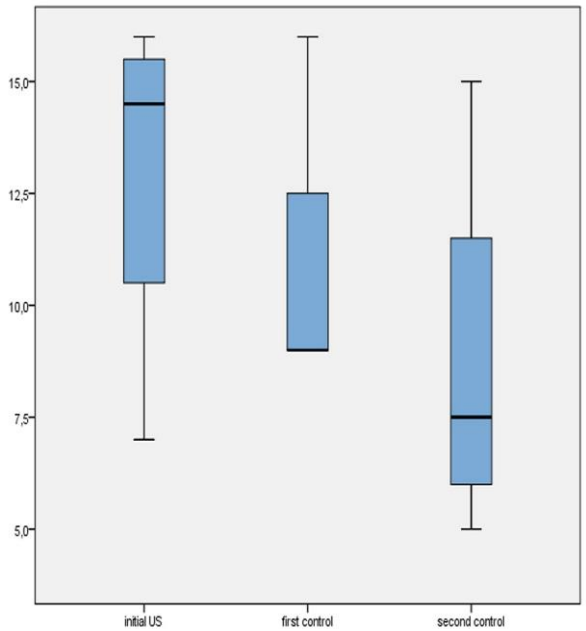

Figure 3: The short axis of the lymph nodes in the first US and control examinations.

A common although the minor effect of the COVID-19 vaccine is unilateral axillary lymphadenopathy. The European Society of Breast Imaging (EUSOBI) offers the following suggestions with the aim of standardizing management and cut back on unnecessary invasive and further imaging procedures: (a) Patients with a history of breast carcinoma should receive vaccination in the thigh or opposite arm; (b) Before breast imaging, vaccination history should have been obtained; (c) Breast imaging examinations should be performed preferably before or at least 12 weeks after immunization procedure; (d) Regardless of vaccination status, follow standard imaging protocols for patients with recently identified breast carcinoma; (e) in cases of axillary lymphadenopathy that is symptomatic or unrelated to vaccination, thoroughly image the other axilla and breasts to rule out carcinoma; (f) in cases of axillary lymphadenopathy on the side that was spared from vaccination, follow standard work-up; (g) Depending on the clinical situation, lymphadenopathy on the same side with the vaccination within 12-week-of vaccination can be considered benign or probably-benign in patients without a history of breast carcinoma and no suspect radiologic results; (h) in patients without a history of breast carcinoma , the immunization adenitis in conjunction with a suspicious breast finding necessitates the standard work-up, including biopsy when appropriate; (i) In individuals with a history of breast carcinoma , notify and treat the immunization adenitis taking into account the amount of time since vaccination and overall risk of nodal metastatic disease; (j) a multidisciplinary team should handle difficult or unclear situations[14].

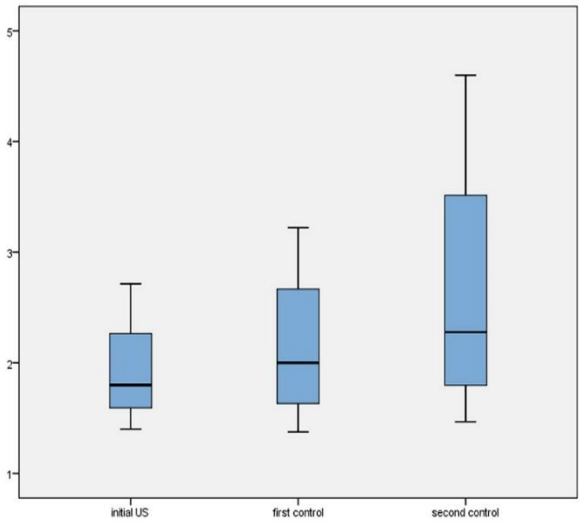

Figure 4: The mean long-short axes ratio of the lymph nodes in the first US and control examinations.

In our clinical practice, whether there were axilla complaints or not, we used a similar approach to patients with abnormal axillary lymph nodes who had received the mRNA COVID vaccine during the previous three months: We advised physical examination, follow-up, US control after a month, and physical evaluation. On the first visit, we recommended a biopsy for a few lymph nodes that were highly suspicious due to size or an obliterated hilum, or an extremely thick cortex. We advised control in the third month after the initial control at the conclusion of the first month. On imaging, the majority of patients were unintentionally discovered. Most people had no complaints. Only 3 patients in our study received a biopsy, and the results were benign. Upon follow-up, the lymph nodes shrunk.

As much as 16 percent of patients who received the COVID-19 vaccine reported having axillary swelling afterward.[15] In a study, 750 patients who received at least one dose of the COVID-19 vaccine within 90 days of either screening or diagnostic mammograms were retrospectively analyzed. It was discovered that 23 (3%) of these patients had axillary adenopathy on mammography, and only 2 of these patients had symptoms.[16] The difference between a rate of 3 percent and 16% is significant. The authors have already mentioned some limitations in this study, such as small sample size, being a single center study.[16] An important limitation is related to mammography. Because mammography shows the lateral axilla well, lymph nodes in the deeper part may not be evaluated with mammography. However, US can show abnormal lymph nodes in the entire axilla[8]. In another study with US, reporting 23 women with COVID-19 immunization adenitis, only 13% of patients had swelling in the axilla[11]. According to their definition, 87 percent of cases were unintentionally found in women who had no symptoms. 18.3% of complaints were documented in our US study, which took place during the rigorous vaccination period, and it was noticed that other individuals had no symptoms. These variations can be connected to the vaccine campaign's time frame. Being aware of the effects of COVID vaccines, we have closely followed the recommendations of EUSOBI and the Society of Breast Imaging (SBI) in our own unit, as well as creating a scheme similar to our pre-COVID axilla management. The median time after the vaccine in patients with adenopathy is significantly shorter at 10 days compared with 18 days in patients without adenopathy[16, 17]. In our study, the mean time after the vaccine is an average of 24 days (1-160 days). The dimensions were statistically considerably reduced in the patients who could be examined after an average of 90 days. After that, there was no discernible difference in the evaluation, which took an average of 191 days. Currently, the SBI advises a BIRADS category 0 initial assignment to allow for additional evaluation of the ipsilateral breast, consideration of a follow-up examination 4–12 weeks after the second dose (BI-RADS 3), and consideration of lymph node sampling to rule out carcinoma if axillary adenopathy persists[11]. When we examined the time frame in which the cases were registered, we discovered that it matched the increase in mRNA immunization (https://ourworldindata.org/covid-vaccinations?country=TUR). Its subsequent decline might be attributed to a heightened awareness of vaccination side effects in particular. Another possibility is that the number of people who are asymptomatic may decline at specific times if there is a gap between repeat immunizations.

5. Conclusions

In conclusion, the immunization adenitis associated with COVID-19 is largely radiologically benign and only significantly enlarged. Patients are typically asymptomatic, and mRNA vaccinations cause axillary lymph node enlargement. Patients and their physicians should be aware of the vaccination and imaging evaluation of specific patient groups considering that these vaccinations will continue to be used for a while in the next years.

Limitations of the Study

The sample size and retrospective methodology of this study were limitations. Additionally, we did not calculate the proportion of patients who underwent various imaging tests at our facilities or comparison between patients who had and did not have immunization.

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Conflict of Interests

The authors declare that there is no potential conflict of interest for the research, authorship, and/or publication of this article. All authors read and approved the final manuscript.

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Author Contributions

AE and MD: design of the study, sample collection, data collection and/or processing, writing the original manuscript.

Ethical Approval

Ethics committee approval was obtained for the study from the Istanbul Medipol University Clinical Research Ethics Committee with the decision dated 02/09/2021 and numbered E-10840098-772.02-4333.

Data sharing statement, Consent to participate and Informed Statement

Waived due to retrospective design.

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Maternal Bisphenol a Levels in Patients Diagnosed with Preeclampsia: A Case-Control Study

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Abstract: This study aims to assess Bisphenol-A levels in serum samples from preeclampsia patients and determine potential distinctions by comparing them against samples from healthy pregnant women. This single-center prospective case-control study aimed to investigate the potential differences in serum Bisphenol-A (BPA) levels between pregnant patients diagnosed with preeclampsia and healthy pregnant women. The study encompassed two distinct groups: the study group consisted of 30 pregnant patients diagnosed with preeclampsia, while the control group included 30 healthy pregnant women matched in terms of gestational weeks and demographic characteristics, maintaining a 1:1 ratio. Serum samples were subjected to analysis using a BPA ELISA kit. The study encompassed a total of 60 patients, who were categorized into two groups: preeclampsia (n=30) and control (n=30). Upon comparison of the BPA values between the two groups, no statistically significant difference was detected (p=0.579). Clear-cut scientific evidence establishing a conclusive causal link between BPA and preeclampsia is still lacking. Further research is needed in this area..

Keywords: Bisphenol A; Preeclampsia; Pregnancy.

1. Introduction

Preeclampsia is a progressive and multisystem disorder that usually occurs after the 20th week of pregnancy or postpartum, with hypertension and proteinuria, or with the significant end-organ-damaging dysfunction of hypertension [1, 2].

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Bisphenol A (BPA) is a synthetic organic compound with the formula (CH3)2C(C6H4OH)2. It is studied under diphenylmethanes and bisphenols [3]. Although BPA dissolves in organic solvents, it is only slightly soluble in water. It has been determined that BPA has an estrogenic effect with hormone-like activity [4, 5]. In addition, different studies have supported it because it causes cancer development by causing epigenetic changes in the tissue [6]. Its abnormal proliferative effect is not only limited to cancer diseases, but it has been shown in the literature that it has a toxic effect on trophoblastic cells. It may cause placentation defects due to aberrant proliferation [7]. Similarly, there are studies showing that it causes placental disorders that mimic hypertensive diseases of pregnancy in animal models [8]. No relation could be established between urinary Bisphenol-A levels in early pregnancy and increased risk of hypertensive disease in advanced gestational patients. Still, it was thought that placental dysfunction could be due to the accumulation of toxic effects [9].

In this study, it was aimed to measure Bisphenol-A levels in serum samples of patients with preeclampsia and to show the possible difference by comparing them with healthy pregnant women.

2. Material and Methods

This single-center prospective case-control study was conducted at a tertiary center from May to July 2023. The study protocol received approval from the Local Ethics Committee and was designed in accordance with the principles of the Declaration of Helsinki.

The study was divided into two groups: the study group comprised pregnant patients diagnosed with preeclampsia, and the control group consisted of healthy pregnant women at similar gestational weeks with comparable demographic characteristics, maintaining a 1:1 ratio. Patients aged 18-45 years, referred to us due to the diagnosis of preeclampsia according to the results of clinical laboratory evaluation, were included in the study. Patients with additional comorbid diseases were excluded from the study. Healthy pregnant patients without a diagnosis of placentation anomaly, gestational hypertension, preeclampsia, and eclampsia were determined as the control group. Blood samples were collected, centrifuged, and stored at -80 degrees Celsius in the laboratory. Control group samples were handled similarly, and after completion of the study groups, thawed samples were analyzed in the laboratory.

The sample number and power analysis required for the research were calculated using G*Power 3.1 software. The study's minimum sample size was 52 when the effect size was 0.5, the alpha error probability was 0.05, the power was 0.8, and the number of groups was 2. The total number of patients was determined as 52 out of 26 cases per group, but considering possible data losses, it was decided to conduct the study with 30 patients per group and a total of 60 cases.

Venous blood samples taken from the patients after 8-12 hours of fasting were centrifuged at 3000 rpm/min for 10 minutes. Serum samples separated into Eppendorfs were stored at -80°C until the study day. BPA level was studied in a Biotek (Elx 800, USA) device using the Sun Red brand, catalog numbered Enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. Optical density was read at 450 nm. The threshold value was calculated according to the manufacturer's instructions. Measurement values were recorded as pg/mL.

2.1. Statistical Analysis

Data analysis was conducted utilizing SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as either mean ± standard deviation or median±range. Normal distribution of data was assessed through Skewness and Kurtosis analysis. Non-parametric variables were compared using the Mann-Whitney U test. A significance level of $p<0.05$ was adopted for all statistical evaluations.

3. Results

Sixty patients were included in the study. The patients were evaluated in 2 groups: preeclampsia, Group I (n=30) and control Group II (n=30). Demographic data and symptoms of the patients are shown in Table 1. The BPA values of the two groups were compared (p=0.579), and no significant difference was observed (Table 2).

4. Discussion

The potential effects of BPA on human health have caused concern among some researchers and health professionals because of its endocrine-disrupting properties [10]. It was thought that BPA might affect hormonal regulation and thus cause pregnancy complications, especially conditions such as preeclampsia [11]. However, there is a lack of conclusive scientific evidence about a definitive causal relationship between BPA and preeclampsia [12]. In our study, in order to explain this relationship, no relationship was found in the results examined.

Dagdeviren et al.'s investigation accentuated the correlation between elevated maternal serum BPA concentrations and the occurrence of preeclampsia. Notably, the preeclampsia group displayed notably higher median BPA levels in comparison to the control group. Intriguingly, an inverse trend was observed, with serum BPA levels showing notable reductions in individuals who underwent delivery at or beyond the 37-week mark, in contrast to those who experienced delivery before 34 weeks due to severe preeclampsia [13]. The absence of a statistically significant contrast in our study may be attributed to certain factors.

Table 1: Demographic and clinical characteristics.

		Group 1 (n=30) Mean (%)	Group 2 (n=30) Mean (%)
	Age(years)	31.8	28.6
BMI			
	Before pregnancy	28.48±5.11	25.42±5.17
	During pregnancy	32.87±5.05	28.91± 5.08
Gravidity			
	Nulligravida	14	10
	Multigravida	11	11
Smoking			
	Yes	6 (20%)	4 (12%)
	No	24 (80%)	26 (78%)
Folic acid			
	Yes	20 (66.7%)	23 (76.7%)
	No	10 (33.3%)	7 (23.3%)
Clinical symptoms			
	None	15 (50%)	30 (100%)
	Vision problems	5 (16.7%)	0
	Severe headaches	5 (16.7%)	0
	Edema	1 (3.3%)	0
	Multiple systemic symptoms	4 (13.3%)	0

Table 2: The relationship of the BPA levels between the groups.

	Group 1 (n=30) Mean	Group 2 (n=30) Mean
BPA Levels	29,25	31,75
	P = 0.579 (p>0,05) Z = -0.554 *	

*Mann Whitney u Tests.

Notably, categorizing preeclampsia severity and its classification based on gestational weeks was not undertaken. Additionally, disparities might arise from the utilization of differing measurement kits. These factors collectively underscore the need for further research to elucidate the intricacies of the observed outcomes.

In the research conducted by Leclerc et al. they explored the concentrations of BPA in a cohort of 58 pregnancies, encompassing 35 normotensive women and 23 women diagnosed with preeclampsia. They employed the advanced technique of high-sensitivity gas chromatography-mass spectrometry (GC-MS) for their assessments. Their findings unveiled the presence of BPA in maternal and fetal blood and within the placental tissue. Remarkably, a substantial aggregation of BPA was detected in the placentas of women afflicted with preeclampsia, particularly when contrasted with the levels found in normotensive women. This study stands as a pioneering endeavor, highlighting a noteworthy link between preeclampsia and the heightened accumulation of BPA within the placental environment [14]. However, it's essential to note that our study, in contrast to Leclerc et al. focused solely on maternal blood serum samples using an ELISA kit and did not encompass the examination of placental tissue. Delving into placental tissue samples might offer further insightful revelations in this domain.

BPA, a chemical widely used in producing polycarbonate plastic found in food and beverage containers, air, and soil, poses risks to human health as it accumulates in various tissues. With hormone-like properties, BPA can bind to estrogen receptors, affecting tumor development. BPA's effects involve numerous transcription factors related to factors such as fat and liver balance, cardiovascular health, and cancer. Lastly, epigenetic changes like DNA methylation, histone modifications, and alterations in microRNA expression contribute to its pathological effects [3]. Considering the increasing rates of plastic use today, more studies can be conducted on the relationship between BPA and hormone-related cancers.

5. Conclusions

In conclusion, the potential impact of BPA on human health, especially its endocrine-disrupting properties, has deserved attention and discussion among researchers and healthcare professionals. The hypothesis that BPA may disrupt hormonal regulation and potentially contribute to pregnancy complications such as preeclampsia has been of interest. However, the current scientific evidence for a definitive causal relationship between BPA and preeclampsia is inconclusive. Our research aimed to shed light on this relationship, but our results did not reveal a significant link.

Limitations of the Study

A larger sample size of the study, including placental tissues, and new studies that will be evaluated by subgrouping according to preeclampsia severity and gestational weeks may provide strong scientific evidence for a possible causal relationship between BPA and preeclampsia.

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Conflict of Interests

None.

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Author Contributions

MAT; Conception, Writer, FE; Data collection, IG; Analysis, GS; Literature Review, IP; Design, NCK; Supervision.

Ethical Approval

Local Ethics Committee, approval number is 2022.05.175.

Data sharing statement

None.

Consent to participate

Consent was obtained from the patient and control groups participating in the study.

Informed Statement

Available.

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Incidence of Obstetric Massive Blood Transfusion and Clinicial Features: Hospital-Based Study

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Abstract: To determine the incidence of obstetric massive blood transfusion in a tertiary center, to determine the characteristics of massive blood transfusion, its main causes and adverse outcomes in obstetric cases, thus trying to contribute to the creation of obstetric emergency plans. The results of 39 cases who underwent massive blood transfusion for obstetric indications were reviewed retrospectively. Demographic data of the cases (age, gravida, parity, body mass index), indications for hospitalization, vital signs during hospitalization, shock index, hemogram values and international normalized ratio (INR) values, massive transfusion indications, transfused blood products (and in intensive care/intensive care units) from patient medical files. Length of hospital stay, reactions and complications related to massive transfusion were recorded. The cases who underwent obstetric massive blood transfusion were divided into 2 groups as low-risk pregnancy and high-risk pregnancy. The data were also compared between the 2 groups. The rate of massive blood transfusion was found to be 26 (12/4607) in 10000 pregnancies in low-risk pregnancies and 1.2% (27/2269) in high-risk pregnancies. Transfusion was started in 21 of 33 cases who underwent cesarean section due to massive bleeding that occurred intraoperatively. The time between the decision of transfusion due to obstetric hemorrhage and initiation of transfusion, and the vital signs and shock indices of the cases at the time of initiation of transfusion were similar between the groups ($p>0.05$). However, while the hemoglobine and hemotocrit levels were statistically lower in the low-risk group at the time of initiation of transfusion, the INR value was statistically higher in the high-risk group. In massive obstetric hemorrhages, which is one of the most important causes of maternal mortality, performing procedures such as blood transfusion and hysterectomy without delay is life-saving. ©2023 NTMS.

Keywords: Massive Transfusion; Obstetrics; Morbidity; Mortality.

1. Introduction

Obstetric hemorrhage remains a common obstetric emergency and is similarly still the leading cause of maternal mortality in Turkey. There are many definitions of massive bleeding in the obstetric literature. Recommended values to consider massive bleeding are, >10 units over 24 h, four units of red

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blood cells (RBCs) transfused within 4 h with active major bleeding of more than 150 mL/min, >8 units of RBCs within 24 h of delivery, Three units RBCs administered over 60 min or postpartum hemorrhage >1500 mL with clinical signs or symptoms of anemia or hemodynamic decompensation [1, 2].

Massive blood transfusion occurs as a 'life-threatening' event when large volumes of blood products are administered over a short period of time, indicates major obstetric bleeding and requires extensive coordination of obstetric, anesthesia and blood bank teams. The incidence of massive blood transfusions related to labor or postpartum hemorrhage (PPH) has been reported to be 0.23-1 per 1000 mothers in high-resource countries [3].

In this study, our aim is to determine the incidence of obstetric massive blood transfusion in our hospital, which is a tertiary center, to determine the characteristics of massive blood transfusion, its main causes and negative outcomes in obstetric cases, thus to contribute to the creation of obstetric emergency plans.

2. Material and Methods

In this descriptive epidemiological study, the results of 39 cases who underwent massive blood transfusion for obstetric indications between 01.10.2022 and 31.05.2023 in our hospital, which is a multidisciplinary 3rd level center, were retrospectively analyzed. Approval was obtained from the Local Ethics Committee for this study (Ethics Committee Approval Number: EK1-2023-297).

The criteria for massive blood transfusion were >10 U within 24 hours or 4 U of Erythrocyte suspension (ES) replacement within 4 hours with active bleeding. Demographic data (age, gravida, parity, body mass index(BMI)), hospitalization indications, vital signs during hospitalization, shock index, hemogram values and international normalized ratio (INR) values, massive transfusion indications, transfused blood products (erythrocyte suspension, fresh blood, frozen plasma, pooled platelet suspension, cryoprecipitate, fibrinogen) and length of stay in the intensive care unit and hospitalization, as well as reactions and complications related to massive transfusion were recorded.

The cases who underwent obstetric massive blood transfusion were divided into 2 groups as low-risk pregnancy and high-risk pregnancy. The following characteristics were used to identify pregnancies as low risk: maternal age 20–39 years, gestational age at delivery 37-42 weeks, BMI <30 kg/m^2, singleton pregnancy, and cephalic presentation. Pregnancies with any evidence of prepregnancy diabetes, gestational diabetes, hypertension, history of preterm birth, poor pregnancy outcome, cervical cerclage, premature rupture of membranes, congenital anomalies (including anencephaly, meningomyelocele/spina bifida, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction defect, cleft lip with or without cleft palate, cleft palate alone, and Down syndrome) accepted as high- risk pregnancy.

2.2.3. Statistical analysis

Statistical analyzes were performed using IBM SPSS 23.0 software. Descriptive and categorical data were expressed as numbers (n) and percentages (%). The results of the continuous data were given as Mean±SD, median, and minimum-maximum values. The mean values of the data according to the groups were calculated using the Independent Sample-T test, and the median values were calculated using the Mann-Whitney test. A p value of <0.05 was considered statistically significant.

3. Results

39 of 6876 deliveries were analyzed in the Obstetrics Unit and Perinatology departments of our hospital during the 8-month period in which cases who underwent massive blood transfusion for critical bleeding due to obstetrics were examined. The need for massive blood transfusion due to obstetrical bleeding was calculated as 5.7 per 1000. While 12 (30.8%) of the cases whose data were analyzed in our study were low-risk pregnancies, 27 (29.2%) were in the high-risk pregnancy category. Thus, the rate of massive blood transfusion was found to be 2.6 (12/4607) in 1000 pregnancies in low-risk pregnancies, and 0.12 in 1000 cases (27/2269) in high-risk pregnancies.

Demographic and clinical data of 39 cases whose data were analyzed in the study are shown in Table 1. When the indications for hospitalization of these cases during the period of obstetric bleeding were examined, the most common indication in the low-risk pregnancy group was a history of previous cesarean section with an uneventful pregnancy (Table 2). In the high-risk pregnancy group, the most common indication for hospitalization was the presence of placenta previa (n=16). 5 of the cases were primigravid (13.2%), 10 of them were primiparous (26.3%), 21 of them were multiparous (52.6%), and 3 of them were grandmultiparous (7.8%). While 8 of 34 cases with a previous delivery history had a vaginal delivery, 10 had a previous cesarean section and 16 had more than one previous cesarean section. While obstetric hemorrhage requiring massive blood transfusion occurred in the third trimester in 25 cases and in the second trimester in 12 cases, it occurred during the first trimester of pregnancy in only 1 case. In one case, it occurred after 24 hours postpartum.

The number of anemic cases (hemoglobine (Hb) <10 g/dl) at hospitalization was 14 (36.8%). In 3 patients, the Hb value was <7 g/dl at the time of admission to the hospital with vaginal or abdominal bleeding.

Table 1: Characteristics of cases who underwent massive transfusion (n=39).

		Mean ±SD	Median (Minimum-Maximum)
Age		32.2±5.2	31.5 (18-42)
BMI (kg/m ^{2})		28.3±4.5	27.7 (17.2-39.4)
Number of pregnancies (n)		3.6±1.9	3.0 (1-9)
Number of births (n)		2.1±1.6	2.0 (0-7)
Week of pregnancy at which bleeding occurs		31.1±7.4	33.2 (13.4-39.6)
Hospitalization	**Hb level (g/dl)**	10.5±2.1	10.5 (5.1-14.0)
	HTC level (%)	32.4±5.7	31.9 (19.8-43.4
	Platelet count (x10 ^{3})	218±72	202 (48-396)
	INR level	1.12±0.42	1.01 (0.90-3.51)
The time between decision of transfusion and starting the transfusion (min)		88±118	37 (7-517)
Total transfusion time (hours)		4.6±1.4	5.3 (1.8- 6.4)
When the transfusion is started	**Systolic BP (mmHg)**	102±19	103 (50-146)
	Diastolic BP (mmHg)	61±14	61 (31-95)
	Heart rate (/min)	107±21	110 (71-80)
	Shock index*	1.1±0.5	1.0 (0.7-2.8)
	Hb level (g/dl)	8.5±1.9	8.3 (4.7-12.1)
	HTC level (%)	26.2±5.4	26.3 (13.9-35.2)
	Platelet count (x10 ^{3})	181±81	173 (18-333)
	INR level	1.13±0.19	1.10 (0.90-1.82)
During obstetric bleeding	**Lowest Hb level (g/dl)**	6.9±1.2	7.0 (3.3-10.0)
	Lowest HTC level (%)	21.5±3.7	21.4 (9.2-30.1)
	Lowest platelet count (x10 ^{3})	114±52	113 (18-249)
	Highest INR level	1.30±0.46	1.20 (0.90-3.51)
On discharge	**Hb level (g/dl)**	10.3±1.4	10.2 (7.6-13.9)
	HTC level (%)	31.7±4.3	31.8 (23.5-42.5)
	Platelet count (x10 ^{3})	294±130	238 (128-752)
	INR level	1.03±0.11	1.00 (0.90-1.39)
Length of stay in intensive care (days)		3.6±3.7	2.0 (1-15)
Length of stay in hospital (days)		13.5±13.2	9.5 (2-65)

*Pulse rate/systolic BP. BMI: Body mass index, Hb: Hemoglobin, HTC: Hemotocrit.

When the demographic data of the cases and clinical findings were compared during the massive blood transfusion process were compared according to the risk status of the pregnant women (low-risk pregnancy group (n=12) and high-risk pregnancy group (n=27) (Table 3). The mean age was significantly higher in the high-risk group as expected (29.0±6.1 versus 33.3±4.7, p=0.023). Body mass indexes were similar in both groups (p= 0.128). The median number of pregnancies in low-risk pregnancies is 3.0 (1-5), median parity is 2.0 (1-4), and in high-risk pregnancies these numbers are 4.0 (2-9) and 2.0 (1-7), respectively (p-value p=0.178 and p=0.178, respectively). p=0.254). While obstetric hemorrhage occurred at 35.2±8.0 (median 38) weeks of gestation in the low-risk pregnancy group, the mean gestational week was 29.4±6.7 (median 28.5) (p=0.035) in the high-risk pregnancy group. The mean Hb, hemotocrit (Htc) levels and INR values at hospitalization were similar between the groups (p>0.05).

Obstetric massive bleeding started during pregnancy in 4 (10.3%) cases, intrapartum in 18 (46.2%) cases, all during cesarean section, and in 17 (43.6%) cases in the postpartum period. The causes of obstetric hemorrhage requiring massive blood transfusion are shown in Figure 1 in detail. While bleeding occurred after vaginal delivery in 5 of the cases with postpartum bleeding, massive bleeding started after cesarean section in 12 cases.

Table 2: Hospitalization diagnoses of patients who received massive blood transfusion (n=39).

	n %
Low-risk pregnancies (n=12)	**30.8**
History of caserean section	**5**
Fetal indications (fetal distress, tachycardia, malpresentation/malposition)	**3**
Oligohydramnios	**1**
Rest placenta	**1**
Pregnancy+anemia	**1**
Early membrane rupture	**1**
High-risk pregnancies (n=27)	**69.2**
Placenta previa	**12**
Placental abruption+intrauterine ex fetus	**3**
Hypertension of pregnancy, severe preeclampsia/Eclampsia/(HELLP) syndrome	**2**
Placenta previa+Placenta accreta spectrum	**2**
Multiple pregnancy	**2**
PPROM	**1**
Placenta previa+Uterine rupture	**1**
Twin pregnancy+Placenta previa	**1**
13 weeks pregnant+acute abdomen	**1**
24 weeks pregnant+acute abdomen	**1**
Pregnancy+Hemophilia C	**1**

Hemorrhage that required massive blood transfusion occurred in the postpartum period in 75% (n=9) of low-risk pregnancies, while 59.3% (n=16) of massive bleeding in high-risk pregnancies was intraoperative (because all were delivered by cesarean section). occurred (p=0.027) (Table 4). The mean time between the decision to transfusion due to obstetric hemorrhage and initiation of transfusion was 88±118 minutes. When the transfusion was started, the mean systolic blood pressure of the cases was 102±19 mmHg, diastolic blood pressure was 61±14, heart rate was 107±21 /min, and the shock index was 1.1±0.5 (median 1.0 median. Shock index was <0.9 in 10 (26.3%) cases, in 18 cases. Transfusion was initiated when it was above the value of 0.9-1.2, and in 11 cases, when the value was higher than 1.2. The time between making the decision to transfusion due to obstetric hemorrhage and starting transfusion and the vital signs and shock indexes of the cases at the time of initiation of transfusion were similar between the groups (p>0.05). While Htc levels were statistically lower in the low-risk group, the INR value was statistically higher in the high-risk group (Table 3).

When the blood groups of the cases were examined, the number of A (+) blood group cases was 18 (47.4%), O (+) n=8, 21.1%, B (+) n=6, 15.8%, AB (+) n=4 (10.4%), A (-) and B (-) are 1 case each. There was no case with O (-) and AB (-) blood groups. When the replaced blood products were examined, similar amounts of ES, Fresh frozen plasma (FFP) and fibrinogen were given to both groups (p>0.05) (Table 5). The median amount of ES given to the low-risk group was 6 (4-10), the median value of FFP was 4 (1-9), the median amount of ES in high-risk pregnancies was 7 (4-15), FFP 4 (2-9) units. (p -value is 0.065 and 0.327, respectively). In low-risk pregnancies, 1 unit of pooled thrombocyte suspension was administered to 2 cases, and 3 units of pooled thrombocyte suspension was administered to only 1 case in high-risk pregnancies. In cryoprecipitate, 10 units were given to 2 cases (3 U in one, 10 U in the other) in low-risk pregnancies and 10 units in 2 cases in high-risk pregnancies. FFP was also given to all patients who were given cryoprecipitate. Fibrinogen (1 g in 2 cases, 2 g in 21 cases, ≥3 g in 9 patients) was given to 32 cases. When the surgical procedures performed in addition to blood transfusion in cases with massive bleeding were examined, the diagnosis was made in 4 cases whose obstetric bleeding started during pregnancy at 13 weeks of gestation. Total hysterectomy was performed directly on the case with uterine rupture before the pregnancy was terminated. Peripartum hysterectomy was performed after cesarean section in 3 cases whose bleeding started during pregnancy. Peripartum hysterectomy was performed in 9 and postpartum hysterectomy was performed in 1 of 18 patients who started perioperative bleeding during cesarean section.

Laparotomy was performed in only 1 of 5 cases with postpartum bleeding after vaginal delivery and hysterectomy was not required in any case. Relaparotomy was performed in 10 of 12 cases with postpartum bleeding after cesarean delivery. While postpartum hysterectomy was performed in 3 of these cases, bleeding was controlled with uterus-sparing surgical procedures in the remaining cases. Transfusion was started in 21 of 33 cases who underwent cesarean section due to massive bleeding that occurred intraoperatively. In 9 of these cases (42.9%; 9/21), bleeding was stopped perioperatively without the need for additional surgical intervention, but postoperative relaparotomy was performed in one of them and hysterectomy was performed. However, peripartum hysterectomy was performed in all 12 cases with perioperative bleeding (Figure 1).

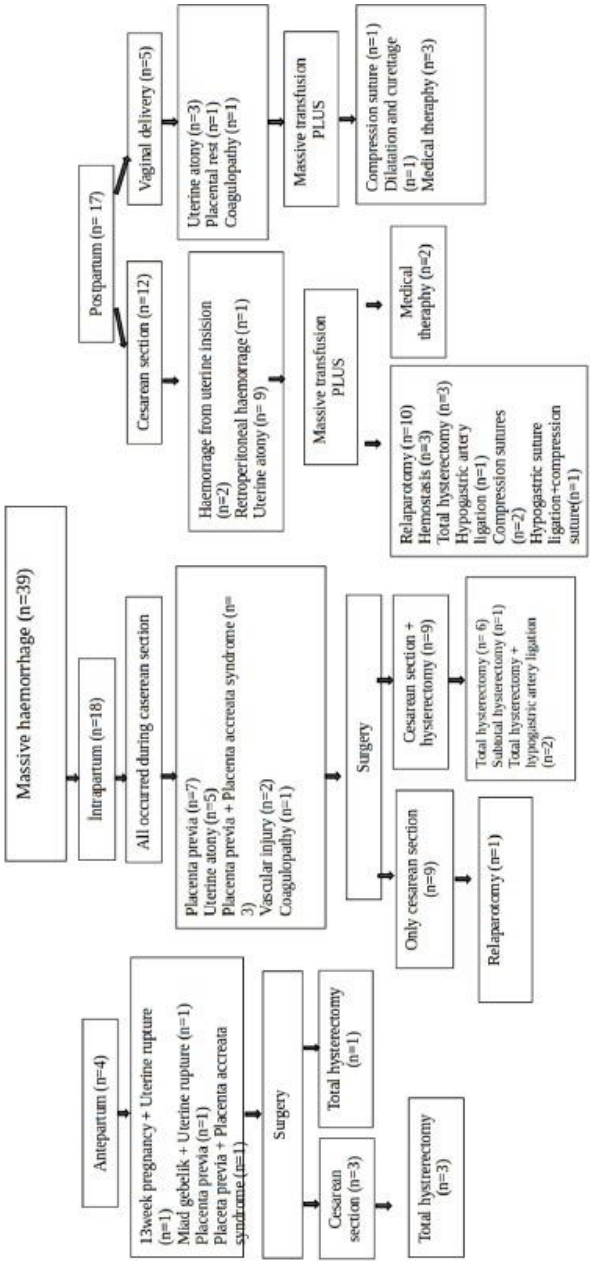

Figure 1: Management chart of cases who had massive blood transfusion and delivered by cesarean section.

Transfusion-related allergic reaction was observed in 7 (17.9%) of the patients who received massive blood transfusion. Febrile nonhemolytic transfusion reaction (high fever; >38 ºC) occurred in 5 of them, acute hemolytic transfusion reaction occurred in 1 case (fever, chills, chest and back/low back pain), and allergic reaction (dyspnea, urticaria) occurred in 1 case. In these cases, transfusion was temporarily suspended and continued after medication. No anaphylactic reaction was observed in any case severe enough to cause the termination of transfusion. In one case in the high-risk pregnancy group, a diagnosis of Transfusion-related acute lung injury (TRALI) was made and treated based on the examination of the development of respiratory distress, hypoxia and hypotension during transfusion and the findings of abnormal chest X-ray.

When the duration of intensive care and hospitalization of the cases were examined, it was observed that the length of stay in the intensive care unit was similar in the two groups (median 1.0 (1-4) days in the low-risk group, 2.5 (1-15) days in the high-risk group, p=0.182). The total length of hospital stay was statistically significantly longer in the high-risk group (median 5.0 (2-21) days in the low-risk group, 10.0 (4-65) in the high-risk group, p=0.044). No maternal death was noted in any of the cases.

4. Discussion

In this study, the incidence of massive blood transfusion due to obstetric hemorrhage in a tertiary center was found to be 5.7 per 1000. This rate was found to be 0.12 per 1000 in high-risk pregnancies. It is noteworthy that 66.7% of the cases who underwent massive blood transfusion due to obstetric hemorrhage had at least one previous cesarean delivery history.

In the literature, many different definitions have been made the definitions of massive bleeding regarding and massive blood replacement. These are usually the definitions made on the unit of blood products. In the Patient Blood Management Guide published by the Ministry of Health of our country, massive transfusion for adults is considered if more than half of the blood volume is transfused within 4 hours or more than the total blood volume (approximately 70 ml/kg of blood volume in adults) within 24 hours [2]. Although this definition is better to eliminate the heterogeneity between the body mass indexes of individuals and to provide standardization, we preferred to use the definitions made by using the unit since our study only used the data of pregnant women and made a retrospective analysis. When pregnancy and delivery are included, the need for blood and blood products transfusion varies between 0.03-0.6 per 1000 cases [3-5]. Common risk factors have been found in many studies that lead to the need for blood product transfusion during pregnancy and labor [5, 6]. These factors include placental pathologies (placenta previa, insertion anomaly, abruption, rest placenta), anemia, excessive uterine distension (multiple pregnancy, polyhydramnios), preeclampsia/eclampsia, preterm labor, induction of labor, trauma, emergency cesarean section and operative delivery.[7] Postpartum hemorrhages are one of the most important risk factors for blood transfusions, as demonstrated in etiological studies on obstetric transfusions [6, 7].

Table 3: Comparison of demographic data and clinical findings by groups.

		Low risk pregnancy (n=12)	High-risk pregnancy (n=27)	p
		Mean±SD (min-max)		
Age		29.0±6.1 (18-37)	33.±4.7 (26-42	**0.023**
BMI (kg/m2)		30.1±3.8 (23.9-35.8)	27.7±4.7 (17.2-39.4)	0.128
Number of pregnancies (n)		2.8±1.5 (1-5)	3.9±2.1 (1-9)	0.136
Number of births (n)		1.8±0.9 (1-4)	2.6±1.6 (1-7)	0.191
Gestational week at the time of bleeding		35.2±8.0 (13-39)	29.±6.7 (17-38)	**0.035**
Hospitalization	Hb level (g/dl)	9.9±2.8 (5.1-13.1)	10.6±1.9 (7.1-14.0)	0.351
	HTC level (%)	31.4±6.9 (19.8-39.2)	32.3±5.6 (20.8-43.4)	0.665
	INR level	1.1±0.1 (0.9-3.5)	1.2±0.7 (0.9-1.4)	0.298
	Platelet count (x10 ^{3})	231±65 (131-332)	212±74 (48-396)	0.450
Duration between the decision of transfusion and starting the transfusion (min)		98±110 (8-373)	8±122 (7-517)	0.785
Total transfusion time (hours)		4.6±1.3 (2.3-6.0)	4.7±1.4 (1.8-5.8)	0.797
When the transfusion is started	Systolic BP (mmHg)	101±16 (70-128)	102±21 (50-146)	0.895
	Diastolic BP (mmHg)	61±13 (40-88)	61±15 (31-95)	0.961
	heart rate (/min)	111±16 (82-138)	105±22 (71-180)	0.408
	Shock index*	1.1±0.3 (0.7-1.8)	1.1±0.5 (0.5-2.8)	0.862
	Hb level (g/dl)	7.4 ±1.2 (5.5-9.0)	8.9±2.0 (4.7-12.1)	**0.022**
	HTC level (%)	23.6±3.7 (18.7-28.7)	27.1±5.8 (13.9-35.2)	0.033
	Platelet count (x10 ^{3})	200±77 (68-330)	174±82 (18-333)	0.366
	INR level	1.0±0.1 (0.9-1.2)	1.2±0.2 (0.9-1.8)	**0.034**
Obstetric bleeding	Lowest Hb level (g/dl)	6.3±0.8 (5.1-7.6)	7.2±1.3 (3.3-10.0)	0.040
	Lowest HTC level (%)	20.3±2.0 (17.2-24.0)	21.9±4.1 (9.2-30.1)	0.227
	Lowest platelet count (x10 ^{3})	134±56 (68-249)	107±49 (18-234)	0.139
	Highest INR level	1.4±0.7 (0.9-3.5)	1.3 ±0.3 (0.9-2.1)	0.508
On discharge	Hb level (g/dl)	9.7±1.1 (7.6 – 11.1)	10.6±1.5 (8.1-13.9)	0.070
	HTC level (%)	30.6±3.4 (23.5-35.9)	32.2±4.6 (24.6-42.5)	0.284
	Platelet count (x10 ^{3})	297±116 (128-478)	287±137 (131-752)	0.841
	INR level	1.0±0.1 (0.9-1.2)	1.0±0.1 (0.9-1.4)	0.495
Length of stay in intensive care (days)		1.8±1.5 (1-4)	4.1±4.0 (1-15)	0.277
Length of stay in hospital (days)		8.5±6.2 (2-21)	15.4±14.7 (4-65)	**0.047**

*Pulse rate/systolic BP. BMI: Body mass index, Hb: Hemoglobin, HTC: Hemotocrit.

Table 4: Period in which massive bleeding occurs according to pregnancy risk groups.

	During pregnancy (n=4)	Intrapartum/Intraoperative (n=18)	Postpartum (n=17)
Low risk pregnancy (n=12)	1 (25.0%)	2 (16.7%)	9 (75.0%)
High-risk pregnancy (n=27)	3 (11.1%)	16 (59.3%)	8 (29.6%)

Table 5: Amount of transfused blood products.

	All cases (n=39)	Low risk pregnancy (n=12)	High-risk pregnancy (n=27)	p
	Mean±SD (Median; Min-Max)	Mean±SD (Min-Max)		
Erythrocyte suspension (U)	7.2±2.7 (6.5; 4-15)	5.9±2.1 (4-10)	7.6±2.8 (4-15)	0.073
Fresh frozen plasma (U)	4.9±2.5 (4.0; 2-11)	4.3±2.4 (1-9)	5.1±2.4 (2-11)	0.361
Fibrinogen (g)	2.1±1.3 (2.0; 0-6)	2.4±0.9 (1-4)	2.5±1.0 (1-6)	0.801

In massive blood transfusion protocols, it is generally recommended to replace blood products as 1 U ES/1 U FFP/1 U pooled platelet suspension [8, 9]. However, in our study, it is seen that the recommendation of 1/1/1 was not fully met in both the low-risk pregnancy group and the high-risk pregnancy group. It is seen that the amount of replaced ES is approximately 2.3 U more than the FFP. Cryoprecipitate replacements were also made in 4 cases who had already been given FFP. Platelet replacement was performed in only 3 cases whose platelet count fell below 50 thousand during surgery. Since there was no maternal mortality despite this practice and all our patients were discharged, it may be considered to review the 1:1:1 recommendation for massive transfusion and to decide on the number of routine applications of platelet replacement. Although the retrospective nature of our study limits its value in this respect, our proposal needs to be supported by prospective and population-based studies.

Another conclusion that can be drawn from this study is the importance of starting blood transfusion when the mother's compensation mechanisms are still active. In the cases in our study, when transfusion was started, mean systolic BP was 102±19 mmHg, diastolic BP was 61±14, heart rate was 107±21/min, and shock index was 1.1±0.5 (median 1.0). It was initiated when the shock index was below 1.2 in 72% of the cases. In massive hemorrhages, while compensation mechanisms are still in effect, it is life-saving to decide on transfusion in a timely manner before hypovolemia symptoms worsen and the severity of coagulopathy does not increase.

Transfusion is a life-saving procedure in the prevention of maternal mortality and morbidity [10, 11]. However, approximately 1% of all transfusions may cause sudden onset or delayed reactions despite the measures taken to reduce the risks [12]. Allergic reactions, hemolytic reactions, blood-transmitted infections, transfusion-related acute lung injury, electrolyte disturbances (hypocalcemia, hypomagnesemia, hyperkalemia), massive transfusion-related complications (hypothermia, metabolic acidosis, and coagulation disorders) limit the clinician in random use of blood products. necessary complications [13- 15]. Considering the risks of blood transfusion, in most clinics, blood transfusion is primarily planned in symptomatic patients with Htc <20%, but in hemodynamically stable and asymptomatic patients with Hb below 7 g/dl, an individualized treatment with oral antianemic or intravenous iron therapy can be used as an alternative to transfusion [16- 18].

The incidence of obstetric massive blood transfusion is increasing, but the rate of hysterectomy and bleeding disorders is decreasing among women undergoing it [19, 20]. In order to minimize the incidence of obstetric massive transfusion, more importance should be given to education on the importance of antenatal visits, evidence-based transfusion practices, multiparous women in advanced age, uterine atony, severe anemia and placenta previa. Appropriate blood transfusion preparations and antenatal early detection for high-risk pregnant women can improve outcomes and reduce adverse outcomes.

5. Conclusions

In massive obstetric hemorrhages, which is one of the most important causes of maternal mortality, application of surgical procedures (compression sutures, arter ligation or hysterectomy) combined with massive blood transfusion is life-saving.

Limitations of the Study

Several limitations to this pilot study need to be acknowledged. These findings are limited by the use of a observational design. The lack of larger sample size adds further caution regarding the generalisability of these findings.

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Conflict of Interests

No conflict of interest was declared by the authors.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version. Conception-İ.Ö.; Design-İ.Ö.; Supervision-H.L.K.; Funding-İ.Ö.; Materials-İ.Ö.; Data collection and analysis-H.L.K; Analysis and interpretation- İ.Ö., H.L.K.; Literature review-İ.Ö.; Writing-İ.Ö.; Critical review-İ.Ö., H.L.K.

Ethical Approval

The study was carried out with the permission of Ethical Committee of Ankara Etlik City Hospital (Decision no: EK1-2023-482).

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate and Informed Statement

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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The Role of Prognostic Nutritional Index in Predicting Multivessel Disease in Patients with ST-Segment Elevation Myocardial Infarction

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Abstract: Acute coronary syndromes (ACS) are common diseases and one of the most common causes of death in the world. The most feared ACS is ST segment elevation myocardial infarction (STEMI). Approximately 50% of STEMI patients have lesions in multivessel disease (MVD), and this is associated with poor outcomes. In this study, we aimed to evaluate prognostic nutritional index (PNI) in patients with STEMI and MVD. 1708 patients diagnosed with STEMI were included in the study. The patients' blood parameters, electrocardiography and echocardiography findings, coronary angiography images were recorded and calculations were made. The mean follow-up period was 38.8±10.3 months. The mean age of 1708 patients was 56.7±12.3 years, and 1370 (80.2) of the patients were male. Lower PNI was associated with MVD (+). Mortality was observed more in the MVD (+) group ($p<0.001$). In addition, PNI was observed to be negatively correlated with the Syntax Score (SS), which indicates vascular severity ($r=-0.347$). In STEMI patients, PNI can predict high SS and be used as an indicator of MVD. ©2023 NTMS.

Keywords: ST elevation Myocardial Infarction; Multivessel Disease; Prognostic Nutritional Index; Mortality.

1. Introduction

Cardiovascular diseases are the most common cause of death worldwide. Coronary artery disease (CAD) is responsible for most of these deaths [1]. Acute coronary syndromes (ACS) are a form of CAD that require urgent intervention [2]. Due to the pharmacological treatment and reperfusion strategies developed in recent years, morbidity and mortality have decreased. However, ACS still remain a frightening reality. ACS include ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP) [2]. STEMI is the most feared scenario among CAD diagnoses because it has a high risk of resulting in mortality if urgent percutaneous coronary intervention (PCI) is not performed. Coronary angiography (CAG) has been used successfully for a long time in the treatment of STEMI. During CAG, infarct related artery (IRA) is intervened, but approximately 50% of the patients may have lesions in many different vessels. Multivessel disease (MVD) is defined as significant stenosis (>70%) in two or more major coronary arteries of 2.5 mm diameter or more [3] and this is associated with poor outcomes [4]. In the presence of MVD, the clinician's treatment method may vary depending on the patient's general condition, hemodynamics and lesion characteristics. Bainey et al showed that complete revascularization reduced cardiovascular death compared with revascularizing the IRA alone [5]. Similarly, complete revascularization is recommended in ACS patients [2]. However, data on how and when this

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should be done are not yet clear. In order to decide the revascularization strategy (IRA PCI, multivessel PCI), the patient's hemodynamics, clinical status and comorbidities, such as hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), along with the complexity of their disease, should be evaluated, following the principles of myocardial revascularization management. In the current guideline, in the presence of MVD in STEMI patients, coronary intervention is recommended at the index procedure or within 45 days [2]. Therefore, starting the procedure by predicting the presence of MVD will provide a significant advantage to the clinician. This prediction will enable the clinician to make faster and more accurate decisions about the patient and choose the right equipment.

It has been shown that both nutritional parameters and inflammatory pathways play a role in CAD [6]. Prognostic nutritional index (PNI) is a new marker that reflects both nutritional status and inflammatory status, calculated based on serum albumin levels and lymphocyte count [7]. The PNI was calculated as 10× serum albumin (g/dl)+0.005× total lymphocyte count (per mm^3). Nutritional status is related to atherosclerosis and the severity of coronary artery disease [8]. Similarly, recent studies have emphasized that inflammation plays a major role in the initiation and progression of atherosclerosis [9]. Therefore, it is thought that PNI, which is a marker that shows both nutritional status and inflammation, may be associated with CAD. In our study, we aimed to evaluate PNI in predicting MVD in STEMI patients.

2. Material and Methods

2.1. Study Population

Patients who applied to our tertiary center between 2015 and 2022 and had ST segment elevation on their (ECG) were included in the study. The definitive diagnosis of STEMI was established by the typical clinical and ECG findings. Patients with non-ST-elevation acute coronary syndromes such as NSTEMI and UAP, patients with false ST segment elevation on ECG, cancer patients and patients with inflammatory diseases were excluded from the study. 1708 STEMI patients who received a definitive diagnosis and were hospitalized for treatment were included in the study. The study protocol was approved by the local institutional ethics committee, and written informed consent was received from each patient.

2.2. Electrocardiographic and angiographic analysis

For ECG examination, 12-lead ECG (10 mm/mV and 25 mm/s) records at admission were used. (Cardiofax V, Nihon Kohden Corp., Tokyo, Japan) The diagnosis of STEMI was made as determined by current guidelines [10, 11]. During admission, blood samples were taken from the peripheral vein and hemogram parameters and biochemical parameters were studied from these blood samples. Since patients with ST elevation on their ECG required urgent revascularization, they were taken to the coronary angiography (CAG) laboratory without waiting. CAG was performed using the Seldinger technique using the femoral or radial route (whichever is appropriate for the patient). Treatment methods are left to the clinician's choice depending on the location and characteristics of the lesion. Multivessel disease (MVD) is defined as significant stenosis (>70%) in two or more major coronary arteries of 2.5 mm diameter or more. The SYNTAX score was derived from the summation of the individual scores for each separate lesion defined as ≥50% luminal obstruction in vessels ≥1.5 mm and all other lesion characteristics considered in the SYNTAX score have an additive value.

The SYNTAX scores were calculated for all patients using dedicated software (available at http://www.syntaxscore.com/calc/start.htm). After CAG, the patients were taken to the coronary intensive care unit and monitorized. In addition, the patient's past disease information, physical examination findings, blood tests, ECG and echocardiography (ECHO) data were obtained from hospital records. Death status was learned from hospital records or ÖBS (Turkish Ministry of Health death notification system) records

2.3. Statistical analysis

SPSS Statistics for Windows, Version 22.0 (SPSS Inc. Chicago, IL, USA) was used for all statistical analyses. For categorical variables, percentages were used. Continuous variables were presented as mean±standard deviation or median (interquartile range) depending on their suitability for normal distribution. Parametric variables were evaluated with the t test, and categorical variables were evaluated with the chi-square test. Mann-Whitney U test was used in the analysis of variables that did not comply with normal distribution. ROC curve analysis was performed to find the PNI cut-off value. Additionally, pearson correlation analysis was applied to determine the correlation between PNI and Syntax Score (SS). Variables with a p value <0.05 were considered statistically significant.

3. Results

The mean age of 1708 patients was 56.7±12.3 years, and 1370 (80.2) of the patients were male. The mean follow-up period was 38.8±10.3 months. More deaths were observed in the MVD (+) group during follow-up [126 (18.2) vs 91 (8.9), p<0.001]. MVD (+) group was older and had more comorbid diseases than the MVD (-) group (p<0.001 for age, p=0.019 for HT, p=0.034 for DM). As expected, SS was higher in the MVD (+) group (p<0.001). Basal demographic data were given in Table 1.

Table 1: Basal characteristics of the groups.

Variables	MVD (+) (n=689)	MVD (–) (n=1019)	p
Age (year)	59.1±11.7	55.1±12.3	**<0.001**
Gender (male,%)	538 (78.1)	832 (81.6)	0.070
Smoker (n,%)	354 (51.4)	582 (57.1)	**0.019**
HT (n,%)	307 (44.6)	387 (38)	**0.007**
DM (n,%)	180 (26.1)	221 (21.7)	**0.034**
COPD (n,%)	38 (5.5)	50 (4.9)	0.577
Syntax Score	19.7±4.8	14.5±2.9	**<0.001**
EF (%)	46.6±8.4	47.6±8.1	0.041
Glucose (mg/dL)	159.9±84.8	143.9±68.4	**<0.001**
Creatine (mg/dL)	0.98±0.47	0.91±0.45	**<0.001**
Hemoglobin (g/dL)	13.5±1.9	13.8±1.7	**0.007**
WBC (10^3/μL)	12.3±3.9	12.4±3.6	0.423
Lymphocyte (10^3/μL)	1.89±0.9	2.01±1.09	0.101
Platelet (10^3/μL)	255.3±68.1	259.5±65.3	0.127
Albumin (g/dL)	3.68±0.49	3.77±0.49	**0.003**
PNI	46.2±7.1	47.8±8.1	**0.005**
CRP (mg/L)	12.3 (6.5-18.7)	9.2 (5.3-15.7)	**<0.001**
Troponin I (ng/mL)	2.1 (0.78-4.86)	1.89 (0.7-4.56)	0.279
Total cholesterol (mg/dL)	177.8±43.6	178.8±44.4	0.828
LDL cholesterol (mg/dL)	113.9±37.9	114.2±39.4	0.991
HDL cholesterol (mg/dL)	38.7±12.3	38.9±12.4	0.606
Triglyceride	137.3±83.1	138.7±96.3	0.425
Follow-up (month)	38.9±11.1	38.7±9.7	0.365
Mortality (n,%)	126 (18.2)	91 (8.9)	**<0.001**

When blood parameters were examined, it was observed that hemoglobin was lower and glucose and creatinine were higher in the MVD (+) group compared to the MVD (-) group (p=0.007, p<0.001, p<0.001, respectively). In terms of inflammation parameters, albumin was lower and CRP was higher in the MVD (+) group compared to the MVD (-) group (p=0.003, p<0.001, respectively). Similar to albumin, PNI was significantly lower in the MVD (+) group (p=0.005). Basal demographic data were given in Table 1.

We performed ROC analysis to find the PNI cut-off value in our cohort and determined the cut-off value of 46.5. In Kaplan-Meier survival analysis with patients below and above this value, it was seen that the survival of patients with low PNI was lower (p<0.001). The Kaplan-Meier analysis is shown in Figure 1.

SS increases with the number of affected vessels and existing lesions. In this case, SS is expected to be high in the group with MVD (+). However, in some single-vessel diseases, SS may be high depending on the lesion location and characteristics. Therefore, correlation analysis was performed between PNI and SS, and it was determined that PNI and SS showed a negative correlation (r:-0.347, p<0.001). The correlation analysis chart is given in Figure 2.

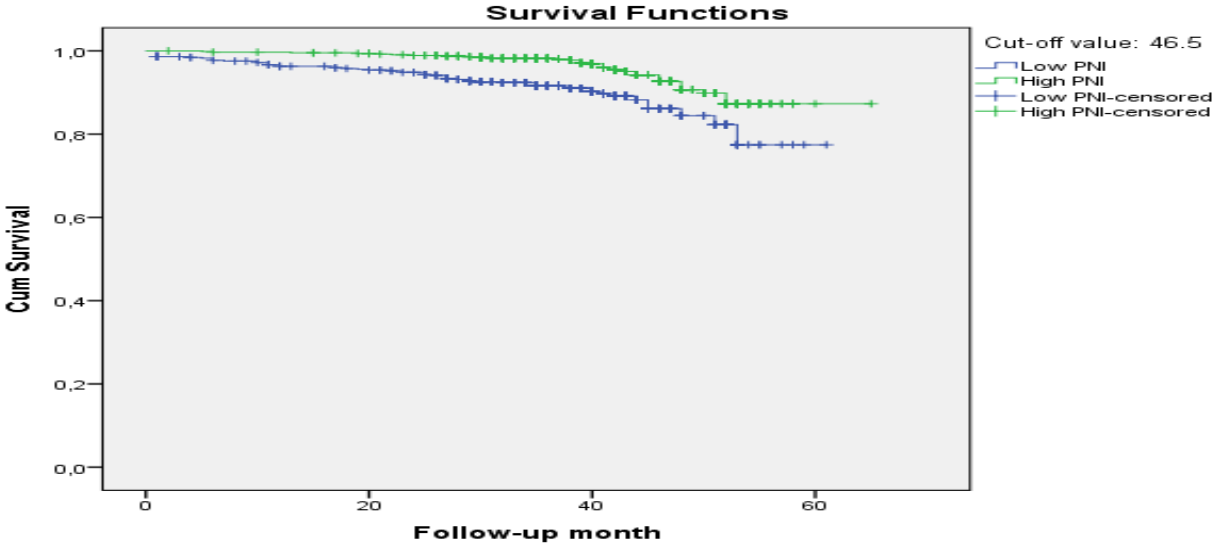

Figure 1: Kaplan-Meier survival analysis according to PNI cut-off value.

4. Discussion

This study showed that patients with MVD (+) had a higher mortality rate during follow-up. Moreover, PNI and MVD were related and there was a negative correlation between PNI and SS.

The SS was designed to predict the postprocedural risk associated with PCI or surgical revascularization. It is a visual estimate of CAD severity and complexity. The SS takes into account complex lesions including bifurcations, calcification, thrombus, chronic total occlusions, and small diffuse disease. The score ranges from 0 to greater than 60 in very complex coronary anatomy lesions [12]. Guidelines recommend using this score when making revascularization decisions [13]. This score can also be used to predict major adverse cardiac events after PCI [14]. In the present study, it was observed that MVD was associated with SS, and in addition, low PNI was correlated with high SS.

CAD prevalence increases with ageing [15]. Studies demonstrated a high prevalence of obstructive CAD in elderly, often with features of advanced disease [16]. In addition, comorbid diseases such as HT, DM, COPD are very common in patients with CVD [17]. In our study, in accordance with the literature, the MVD (+) group was older and had more comorbid diseases.

Having anemia in the patient can mimic the symptoms of CAD, also anemia is also associated with CAD [18]. Similarly, it was found to be related to MVD in our study

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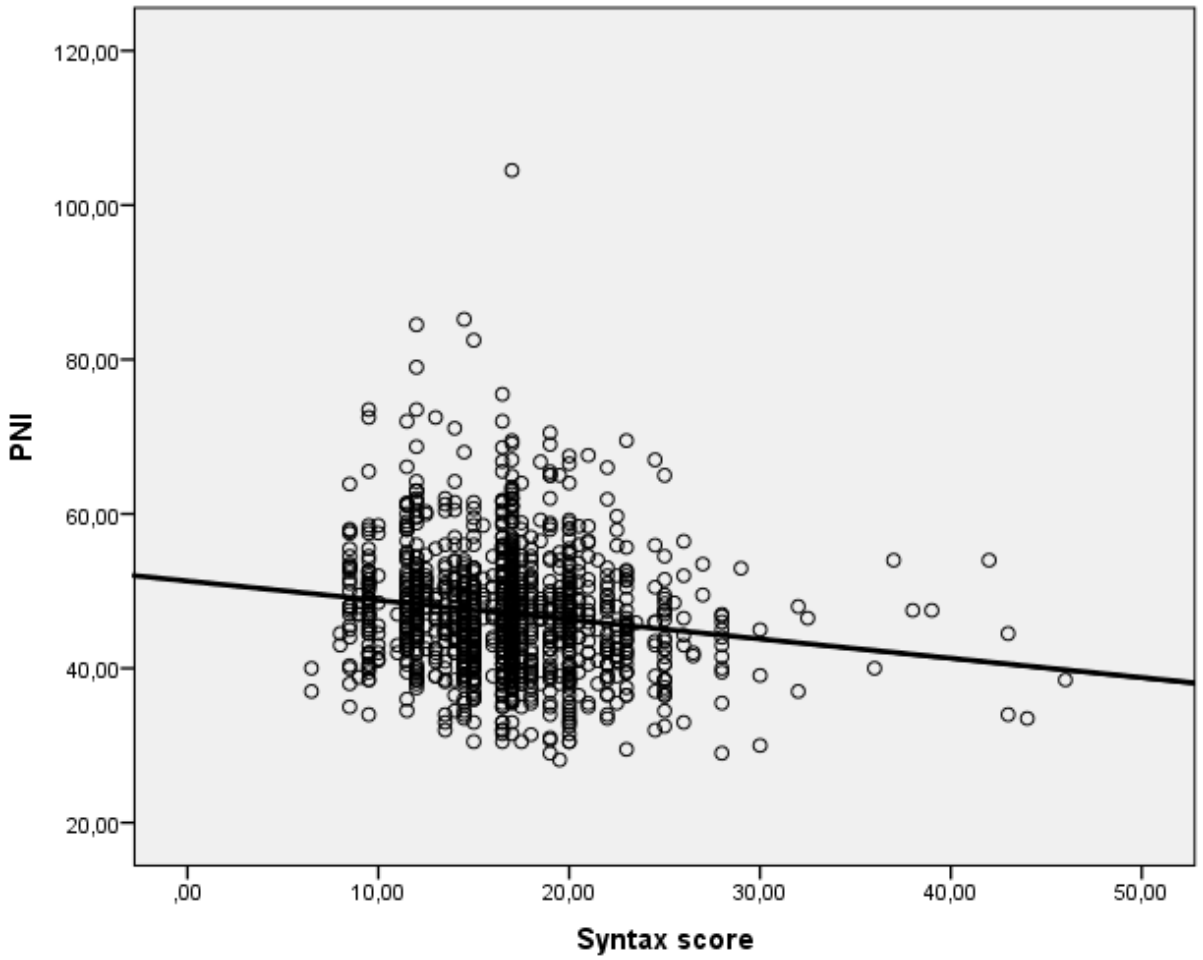

Figure 2: Scatter dot showing negative correlation of PNI and SS.

Serum creatine level is an indicator of kidney functions. The presence of chronic renal failure (CRF) is a major risk factor for developing CAD [19]. Korkmaz et al. showed that creatine level correlated with CAD and was associated with the severity of CAD [20]. Similar to the literature, in the present study, creatine levels were found to be associated with MVD.

In the MVD (+) group, there were more DM patients and the patients' glucose levels were also higher. There is much evidence that DM disease is associated with CAD, and MVD is more common in DM patients [21]. Studies shown that hyperglycemia is an independent predictor of severe CAD even in non-diabetic patients [22]. In our study, higher glucose level was associated with MVD presence.

In the past few years, the role of inflammation in the development and progression of atherosclerosis has been better understood, thus inflammatory biomarkers

are now used more increasingly in CAD screening and prognosis [23]. Among these, the most easily accessible and frequently used ones are hemogram parameters, C-reactive protein (CRP) and albumin. Studies suggest that low lymphocyte count plays role in atherosclerosis, and is associated with worse outcomes in patients with cardiac disease such as heart failure, chronic ischemic heart disease and acute coronary syndromes [24]. Additionally, albumin and CRP are also associated with CAD and disease severity [25, 26]. Albumin is an important parameter for showing nutritional status as well as inflammation. Since nutritional status is related to CAD, albumin becomes even more important [6, 8]. Considering the role that both inflammation and nutritional status play in atherosclerosis and CAD, PNI, which combines these two conditions, can be considered a more specific parameter. Studies have shown the relationship between PNI and CAD [27]. Akbuga et al. showed that PNI, was a predictor of coronary collateral development [28]. A small-scale study with a short follow-up period including ACS patients demonstrated the relationship between coronary artery severity and PNI [29]. In our study with a long follow-up period and including 1708 ACS patients, we showed that there was a significant relationship both between PNI and MVD and between PNI and SS.

5. Conclusions

PNI, which indicates nutritional status and inflammation, is a useful parameter that can be easily calculated. In this context, PNI can be used to estimate the prevalence and severity of coronary artery disease.

Limitations of the Study

The main limitation of our study was the study was retrospective, therefore the validity of the data is controversial. Second, since the clinician's treatment preferences cannot be randomized, there might be selection bias. Third, the study was conducted in a single center, it may not reflect the society.

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Conflict of Interests

The authors declare no conflict of interest.

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Author Contributions

O.B and E.A conceived and planned the hypothesis and wrote the manuscript. O.B performed the calculations. E.A are responsible for the data and supervised data analyses. All authors supported writing of the manuscript. O.B and E.A designed and directed the current topic. All authors provided critical feedback and helped shape the research, analysis and manuscript. O.B and E.A directed the final version and is responsible for final approval of the submitted manuscript.

Ethical Approval

Ethical committee approval was received from the Ethics Committee of Atatürk University (Approval Date: 07/09/2023; Approval Number: 2023/592).

Data sharing statement

Available upon request from the corresponding authors. The data are not publicly available due to compliance with privacy laws.

Consent to participate and Informed Statement

All data relevant to the study are included in the article. Informed consent was obtained from all participants included in the study.

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Comparison of Treatment Methods of Primary Obstructive Megaureter

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Abstract: Primary megaureter (PM) is a common congenital uropathy. In this study, we compared the results of treatment options for primary megaureter with obstruction in UVJ. The files of all patients who underwent open surgery and had a double J (JJ) ureteral catheter for treatment of primary obstructive megaureter in our institution between 2010 and 2023 were evaluated retrospectively. The demographic information of the patients, the results of imaging tests before and after the surgery, early and late complications after the treatment, and the length of stay in the hospital were recorded. The results of both treatment methods were compared statistically. A total of 23 patients and 26 kidney units over 13 years were retrospectively analyzed. Eighteen patients were male (78%); 5 were girls (22%). Ureteral tapering and ureteroneocystostomy (UNC) were performed with open surgery in 8 patients, while JJ stent was placed in 12 patients primarily by cystoscopy. In the urinary system ultrasonography (USS) performed at an average of 3 months after the treatment, hydronephrosis grades were observed to regress in 25 units. All patients recovered after surgery and there was no significant difference between the two treatment methods ($p > 0.05$). In the treatment of primary obstructive megaureter (POM), endoscopic JJ stenting is as effective as ureteral reimplantation with open surgery. It may be considered more valuable due to the shorter hospital stay. ©2023 NTMS.

Keywords: Double J Stent; Primary Obstructive Megaureter; Pediatric Patient; Ureteroneocystostomy.

1. Introduction

Primary megaureter (PM) is a common disease among congenital uropathies. PM; The presence of an enlarged ureter with or without pelvicalyceal dilatation due to an anomaly at the vesicoureteral junction. Treatment of PMs varies depending on the cause. PMs; It is divided into 3 classes: due to reflux, due to obstruction at the ureterovesical junction (UVJ), and without obstruction and reflux [1].

Treatment of PM due to reflux is mostly shaped by the degree and clinical presentation of vesicoureteral reflux (VUR). In non-reflux PM, symptoms secondary to impaired differential kidney function (DRF) and/or potential impaired urinary drainage are decisive for the treatment strategy [2]. Narrowing of the ureter and reimplantation to the bladder is a traditional treatment for POM that does not resolve or is associated with

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obstruction or pyonephrosis. In recent years, endoscopically placed JJ stents have been used in the treatment of permanent or progressive nonreflux megaureters in children [3]. The use of the endoscopically placed JJ stent to provide internal drainage of the ureters was first described more than 20 years ago [4]. Subsequently, many authors reported the success of double-J stent placement as a safe and effective alternative treatment to external drainage in children [5]. In this study, we compared the results of our treatment methods in patients with primary obstructive megaureter.

2. Material and Methods

After obtaining ethical approval from our institution with the number 2021/252, the files of all patients who underwent open surgery and underwent therapeutic JJ ureteral stent between 2010 and 2023 due to primary obstructive megaureter were evaluated retrospectively. The demographic information of the patients, the results of imaging examinations before and after the treatment, early and late complications, and length of hospital stay were recorded.

The treatment criteria of the patients were as follows;

1. Increasing hydroureteronephrosis with a retrovesical ureter greater than 10 mm with an obstructive drainage pattern on dynamic radionuclide renography or
2. Dynamic radionuclide renography pattern with evidence of dysfunction with less than 40% differential kidney function with an obstructive excretion, or
3. Presence of pyonephrosis / recurrent urinary tract infection.

Patients with a ureteral diameter of 15 mm or more and atrophic kidney underwent an open surgical procedure; an Endoscopic JJ stent placement procedure was applied to patients with ureteral diameter of less than 15 mm.

Ureteral stents used; Plasti-Med was a brand of 3 fr 16 cm with one end closed and 4 fr 18 cm with one end closed. A Karl Storz-Germany 9.5-5 Fr and 8-4 Fr cystoscope were used to place JJ stents transurethrally. In patients who underwent open surgery, the ureter was narrowed and a Glenn ureteroneocystostomy was performed. Antibiotic prophylaxis was administered to patients treated with both methods. While the JJ stents of the patients treated with open surgery were removed after an average of 4-6 weeks; JJ stents inserted through endoscopic or antegrade nephrostomy were removed after 6-8 weeks. The stents were removed endoscopically with an outpatient procedure. Patients were re-evaluated with routine renal system ultrasonography (USS) 3 months after removal of the JJ catheter. If there was increasing hydroureteronephrosis, it was re-evaluated with mandatory dynamic radionuclide renography. Data were evaluated using descriptive statistics showing median values and range. Patients who started the first treatment in another center and then applied to our clinic and patients who discontinued the treatment were excluded from the study.

3. Results

A total of 23 patients and 26 kidney units over 13 years were retrospectively analyzed. Of the patients, 18 (78%) were male; 5 of them were girls (22%). The mean age was 37.7±35.2 months (0-161 months). In girls, the mean age was 69.4 ±67.4 months (2-161 months); the mean age in men was 28.9±28.8 months (0-132 months).

4 of 26 kidney units are right; 16 of them are left; 3 were bilateral. Eighteen patients had recurrent urinary tract infections. 5 patients had antenatal hydroureteronephrosis.

In the urinary system, ultrasonography was performed before the treatment; There was grade 1 hydronephrosis in 1 unit, grade 2 hydronephrosis in 13 units, grade 3 hydronephrosis in 12 units, and ureter diameters were larger than normal and the mean was 14.5±7.5mm (7-25 mm). Vcug was normal in all patients.

In static kidney scintigraphy ((Dimercaptosuccinic Acid (DMSA)) parenchymal function was normal in 8 units, the function was 20% or less in 2 units, and scar appearance was present in 4 units. In 12 units, renal function was 40% and above with mild dysplasia. There was an obstructive pattern in the dynamic radionuclide renography of the patients. Antibiotic prophylaxis was started in all patients during the investigation phase. All patients were treated after an average of 2.9 months (2-15) after admission. Emergency intervention was performed on the patient, and JJ stent was requested by cystoscopy, but when the JJ stent could not be inserted endoscopically, an anterograde JJ stent was inserted together with nephrostomy. 8 patients underwent ureteral tapering and UNC with open surgery, while 12 patients received a JJ stent primarily by cystoscopy.

In the USS performed at an average of 3 months after the treatment, it was observed that the hydronephrosis grades regressed in 25 units. One patient with multiple urinary anomalies also had an increase in hydronephrosis.

Renal hydronephrosis and ureter diameters were compared in preoperative and postoperative ultrasonographic imaging of patients with endoscopic JJ stent implantation and patients who underwent open surgery for ureteral reimplantation. It was observed that all patients recovered after surgery and there was no significant difference between the two treatment methods ($p>0.05$).

While the average hospital stay was 36±8 hours in endoscopic treatment; In the open surgery technique, the mean time was 72±8 hours ($p<0.05$).

Of the 26 units operated for POM; Preoperative and postoperative urinary system ultrasound findings are given in Table 1.

Table 1: 26 units operated for POM; Pre- and postoperative urinary system ultrasound findings.

	JJ stent placed with endoscopic treatment (n=16)	**Treated with open surgery (n=10)**	Test Results
Preoperative degree of renal hydronephrosis			
Grade 1	-	1 (10.0)	
Grade 2	12 (75.0)	2 (20.0)	p>0.05
Grade 3	4 (25.0)	6 (60.0)	X^2=3.610
Grade 4	-	1 (10.0)	
Preoperative ureteral diameter			
Normal	1 (6.3)	2 (20.0)	p>0.05
4-10 mm	2 (12.5)	3 (30.0)	X^2=3.055
11-20 mm	12 (75.0)	5 (50.0)	
21 ve üzeri	1 (6.3)	-	
Postoperative degree of renal hydronephrosis			
Normal	7 (43.8)	4 (40.0)	p>0.05
Grade 1	6 (37.5)	3 (30.0)	X^2=0.114
Grade 2	2 (12.5)	3 (30.0)	
Grade 3	-	-	
Grade 4	1 (6.3)	-	
Postoperative ureteral diameter			
Normal	11 (68.8)	5 (50.0)	p>0.05
4-10 mm	2 (12.5)	3 (30.0)	X^2=0.576
11-20 mm	3 (18.8)	2 (20.0)	
21 ve üzeri	-	-	
Hospital stay time	36±8 hours	72±8 hours	p<0.05

4. Discussion

The traditional treatment of POM is UNC with ureteral constriction. Minimally invasive treatment methods have been used in the last 20 years and have been found to be as effective as UNC. These are endoscopic balloon dilation to the UVJ, which is thought to be narrow, or endoscopic placement of the JJ stent, which is passed through the UVJ and extends to the kidney pelvis. Research has shown that; Balloon dilation performed with endoscopy is a safe and effective method. It can be definitive treatment [6-9]. It was observed that endoscopic balloon dilatation was not used in our series because the equipment was not available. Endoscopic insertion of the JJ stent, which is one of the non-invasive treatment methods, was applied. Patients who developed VUR after endoscopic balloon dilatation procedure have been reported [10]. In our series, no patient developed VUR after the endoscopic procedure.

The only treatment for POM is a cystoscopically placed JJ catheter with limited success. However, in infants, catheter placement has been reported to be a reasonable interim solution until the baby is old enough for a definitive procedure [11]. It has been stated that reimplantation will be more difficult in a small bladder in infants, and it has been observed that endoscopic JJ stenting is recommended for POM in patients in infants [12]. In our study, it was seen that JJ stent was placed in 8 infant patients and UNC was performed in 2 infant patients. In another study, it was stated that ureteral reimplantation with an open method is safe and feasible, although there is an anatomical limitation in infants [13]. In our study, we observed that the endoscopic JJ stent was placed primarily in infant patients

Although it has been stated that cutaneous ureterostomy is safe and usable for the treatment of POM infants [14]. It is not a method used in recent years and it was not a preferred treatment method in our study.

Another study stated that complications caused by JJ stents should also be taken into consideration and should be used only for selected patients [15]. There were no JJ stent-related complications (perforation or increased urinary tract infection) in our series.

It has been stated that endoscopic methods can be primarily evaluated in the treatment of POM, but a larger database is needed to clarify whether they are as effective as open surgery [1]. In this study, we found that there was no significant difference between the two techniques when we compared the ureter diameter and the degree of hydronephrosis in the kidney before and after the endoscopic JJ catheter insertion with the open surgical method (p>0.05). We think that endoscopic JJ insertion may be more valuable due to the shorter hospital stay.

5. Conclusions

In the treatment of POM, endoscopic JJ catheter insertion is as effective as open surgical ureteral reimplantation. It may be considered more valuable due to the shorter hospital stay. Prospective studies with larger numbers of patients are needed to be considered a definitive and only treatment.

Limitations of the Study

This study is retrospective. The number of patients is small and balloon ureteral catheter
dilation was not used among the treatment options.

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Conflict of Interests

The authors declare that there is no conflict of interest.

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Author Contributions

FÖS: Conceptualization and study design; literature search and selection, recruitment, data refinement and extraction, formal analysis; investigation; methodology; project management; resources; verification; visualization; writing – original draft; writing – reviewing and editing. Mehmet Sarıkaya- İÇ: Conceptualization and study design; literature search and selection, data refinement and extraction, formal analysis; investigation; methodology; project management; resources; verification; visualization; writing – original draft; writing – reviewing and editing. MG-TS- İY–HP: Laboratory determinations, original draft, writing – reviewing and editing. FÖS: data improvement and extraction. FÖS-İÇ: writing – reviewing and editing.

Ethical Approval

Ethics committee approval was obtained from the Selcuk University Faculty of Medicine Local Ethics Committee for this study (2021/252).

Data sharing statement

All data pertaining to this study are available in correspondence upon reasoned request through the author.

Consent to participate and Informed Statement

Since this study is a retrospective study, patient consent is not required.

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Gonadotropin Versus Gonadotropin/Letrozole Protocol in Previously Failed Antagonist Cycles in Patients with Low Prognosis

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Abstract: Letrozole is an aromatase inhibitor which has been used for ovulation induction. Our aim is to evaluate the effectiveness of adding letrozole to gonadotropins in early follicular phase of gonadotrophin-releasing hormone antagonist (GnRH-a) protocol poor ovarian-responders who had failed in the preceding GnRH-a cycle. Ninety-eight patients with poor ovarian response who had previously failed GnRH-a cycle were included. Patients (n; 58) who were treated with letrozole plus gonadotropins (LzGA) were compared with patients (n; 40) who only received gonadotropins (GA). The number of total oocytes retrieved, the number of MII oocytes and fertilized oocytes, fertilization and implantation ratios, the rate of cycle cancellation as well as clinical pregnancy and live birth rates**.** LzGA group had a significantly shorter duration of GnRH-a stimulation and higher progesterone level at trigger day (p=0.005, p=0.049 respectively). Letrozole administration demonstrated lower estradiol levels at trigger day and the total dose of gonadotropins used were lower in LzGA group with no significant difference (p=0.13, p=0.13 respectively). Adding letrozole to gonadotropins in GnRH-a protocol in patients with poor prognosis did not improve pregnancy outcomes. But it seems to decrease IVF costs by reducing the GnRH-antagonist and gonadotropin dosage.

Keywords: Letrozole; Gonadotropin; Poor Ovarian Reserve; IVF.

1. Introduction

A third-generation aromatase inhibitor, letrozole, is now considered as a potent ovulation induction agent [1, 2]. The addition of aromatase inhibitors to gonadotropins has been shown to increase pre-ovulatory follicles without any adverse effect on pregnancy outcomes [2]. Recent studies hypothesized that the addition of letrozole to controlled ovarian stimulation protocols will reduce the total gonadotropin dose and decrease the costs of the IVF cycle. Previous studies have investigated the results of using gonadotropins and aromatase inhibitor together or sequentially in patients with low ovarian reserve, but the results are inconsistent [3-10].

We aimed to evaluate whether it is beneficial to add letrozole in the succeeding cycle of previously failed GnRH-a cycles of patients in the specific cohort of poor

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ovarian response including POSEIDON group III and group IV.

2. Material and Methods

2.1. Participant cohort

In our article, a retrospective study was presented, utilizing data collected between June 2018 and August 2021 at the İzmir Tepecik Research Hospital IVF Centre, affiliated with the University of Health Sciences.

Inclusion criteria encompassed patients designated within POSEIDON groups III or IV, and those who had encountered only one previous unsuccessful cycle involving GnRH-a. The patient cohort was divided into two distinct categories: the study group, composed of 58 individuals subjected to LzGA cycles, and the control group (n: 40), who solely underwent gonadotropin administration. Exclusion criteria entailed patients diagnosed with other infertility factors such as polycystic ovarian syndrome (PCOS), tubal factor and male factor infertility. Additionally, we excluded individuals who had more than 6 months interval between the treatment cycles.

The study was approved by the Ethics Committe of the University of Health Sciences Turkey (Protocol Number: 2022/07-14, date: 18.07.2022).

2.2. Ovarian stimulation

During the gonadotropin cycle, recombinant FSH (Gonal-F; Merck-Serono, Istanbul, Turkey) and highly purified hMG (Merional; IBSA, Istanbul, Turkey) were administered at doses varying from 225 to 300 IU daily. The dosage of FSH and hMG were modified in alignment with the ovarian response that was determined by transvaginal sonography and blood E2 measurements. A non-rigid GnRH antagonist protocol (Cetrotide, 0.25 mg per day, Merc-Serono, Istanbul, Turkey) was introduced when leading follicle achieved an average diameter of 14 mm and/or the serum E2 concentration increased above 350 pg/mL. This regimen was sustained until day of human chorionic gonadotropin (hCG) administration. To induce follicle maturation, recombinant hCG in a dose of 250 μg (Ovitrelle; Merck-Serono, Istanbul, Turkey) was administered, once at least three follicles had attained diameter of 17 mm in average.

Within LzGA cycles, hormonal and sonographic assessments were conducted on the second day of the menstrual cycle. Commencing on either day 2 or 3, Letrozole (Femara; Novartis, Istanbul, Turkey) was administered with a daily dose of 5 mg (2.5 mg twice a day) over 5 days. Ovarian stimulation, GnRH-a protocol, and triggering follicle maturation were applied as similar to previous cycles.

Oocytes were retrieved 36 hours subsequent to the administration of the hCG trigger. The retrieved oocyte cumulus complexes underwent a washing process using GMOPS Plus medium, followed by the detachment of cumulus cells bound to the eggs through the application of 80 IU hyaluronidase (Vitrolife). The standard intracytoplasmic sperm injection (ICSI) procedure was performed after removingcumulus cells attached to the oocytes. The ICSI process was carried out by an inverted Olympus microscope (IX 71) equipped with a Narishige micromanipulator (Narishige, Tokyo, Japan) and a heated stage. Sperm selection was conducted under magnification ranging from ×200 to ×400, with focus on selecting sperms displaying nearly normal morphology for injection into the oocyte. Fertilization was evaluated 16-20 hours following insemination, as evidenced by emergence of two distinct pronuclei and two polar bodies. Resultant zygotes were placed into G1 Plus medium (Vitrolife) within an Esco Miri incubator at 37°C (6% CO2, 5% O2, and 89% N2) for subsequent days. Embryo transfer was performed either on third or fifth day of development.

2.3. Outcome measurements

Primary outcomes were categorized based on chemical pregnancy rates, clinical pregnancy rates, and live birth rates. To verify pregnancy, a serum ß-hCG level was assessed on day 12 following transferring embryo. ß-hCG level exceeding 5 IU/L was deemed positive. Confirmation of clinical pregnancy was established when a fetal cardiac heartbeat was detected via transvaginal ultrasound at the 6th week of gestation. The implantation rate was calculated by dividing count of gestational sacs detected on ultrasound by the number of embryos initially transferred. Live birth was defined as delivery of an infant beyond the 24th week of gestational duration.

The secondary outcomes cover a range of measures, including cumulative gonadotropin dose on average, duration of gonadotropin stimulation on average, duration of GnRH antagonist stimulation on average, average serum estradiol concentration on hCG administration day, mean number of retrieved oocytes, mean number of mature oocytes (metaphase II oocytes), mean number of fertilized oocytes (average count of 2 pronuclear zygotes), fertilization rates, and average number of transferred embryos.

2.3. Statistical analysis

Statistical analyses were performed via SPSS for Windows 23.0 (SPSS, Chicago, USA). Results are given as Mean±standard deviation. Continuous variables were analyzed with Student's t-test, while categorical variables were assessed using the chi-square test. A p value <0.05 was considered as statistically significant.

3. Results

Overall, 98 patients identified to have poor prognosis according to Poseidon Classification, were eligible for the study. Of the 41 patients in LzGA group 25 were in Poseidon 3 and 16 were in Poseidon 4 group. Of the 57 patients in GA group 33 were in Poseidon 3 and 24 were in Poseidon 4 group. There was no significant difference according to the Poseidon groups between LzGA and GA. Table 1 summarizes the baseline patient

characteristics. Two groups were comparable with respect to women's age, body mass index, menstrual cycle length, antral follicle count, the duration of infertility as well as AMH levels. Basal FSH, E2 levels and TMSC were similar.

Table 1: Patient characteristics and basal hormone levels between groups.

Parameters	LzGA Group (N=58)	GA Group (N=40)	*P*
Age (years)	34.34±3.96	35.00±3.60	0.40
Body mass index (kg/m^2)	25.56±4.76	24.73±4.54	0.38
Menstrual cycle (days)	26.93±2.82	26.85±2.72	0.89
Paternal age (years)	37.05±6.03	37.63±6.01	0.64
Duration of infertility (years)	6.33±4.75	6.12±4.02	0.84
Total motile sperm count (million)	56.67±55.67	42.28±51.46	0.19
Antral follicle count	4.60±2.56	4.90±2.77	0.59
Serum FSH on day 3 (mIU/ml)	12.68±4.94	11.28±4.42	0.15
Serum LH on day 3(mIU/ml)	4.73±2.26	4.17±2.14	0.21
Sserum E2 on day 3 (pg/ml)	46.09±24.09	43.85±17.22	0.15
Day-3 serum P (ng/ml)	0.80±0.62	0.78±0.42	0.92
AMH (ng/mL)	0.69±0.35	0.64±0.30	0.49
TSH (IU/mL)	1.82±0.93	2.17±2.30	0.30
PRL (ng/mL)	15.47±6.19	14.58±6.31	0.48
Ratio of POSEIDON Group 3	0.60(25/41)	0.57(33/57)	0.83
Ratio of POSEIDON Group 4	0.40(16/41)	0.43(24/57)	0.83

Mean±SD (range) or percentage (number/total); LzGA=letrozole plus gonadotropins; GA= gonadotropins only. Statistical significance: p<0.05. FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, P: Progesterone, AMH: Anti-mullerian hormone, TSH: Thyroid-stimulating hormone, PRL: Prolactin

Ovarian stimulation parameters were compared in Table 2. According to the Table 2, the LzGA group had a significantly shorter duration of GnRH-a stimulation period and higher progesterone levels at trigger day when compared with GA group. Although letrozole administration depicts lower E2 levels at trigger day and lower dose of total gonadotropin use, these results were not statistically significant. Duration of ovarian stimulation, GnRH antagonist starting day and β-hCG application day were comparable.

Table 3 depicts the comparison of cycle outcomes. Mean follicle (>14mm) count, total count of follicles on trigger day, mean number of retrieved oocytes, mean number of metaphase II oocytes, mean number of 2PN zygotes and the top-quality embryos were similar in the two groups. In addition, fertilization and implantation rates, as well as the number of transferred embryo, the day of embryo transfers, and cycle cancelation rates were similar. On the other hand, MII oocyte ratio was higher in LzGA group without statistical significance. Fertilization failure and developmental failure accounted for the majority of the causes of cycle cancellation.

Table 4 shows that fertilization failure and developmental failure accounted for the majority of the causes of cycle cancellation. Degenerated oocytes were the least encountered cause for cycle cancellation.

Pregnancy results is shown in table 5. No significant difference was found in chemical pregnancy, clinical pregnancy, and live birth rates between the groups (*p*-value 0.83, 0.56, and 0.47 respectively).

Table 2: Comparison of ovarian stimulation outcomes between groups.

Variables	LzGA Group (N=58)	GA Group (N=40)	p-Value
Duration of ovarian stimulation (days)	8.12±2.16	8.18±2.22	0.90
The total dosage of Gonadotropins (IU)	2293.33±731.00	2534.38±827.27	0.13
Antagonist starting day	7±2.74	6.15±2.08	0.10
Duration of Antagonist Usage (days)	3.91±1.41	5.03±2.39	0.005
hCG trigger day	10.21±2.60	10.18±2.24	0.95
E2 level at hCG day (pg/ml)	711.37±866.87	955.90±714.27	0.13
Progesterone level at hCG day (ng/ml)	1.23±1.37	0.79±0.35	0.049
LH level at hCG day (mIU/ml)	3.18±2.72	3.02±2.12	0.36

Mean±SD (range) or percentage (number/total); LzGA=letrozole plus gonadotropins; GA=gonadotropins only. Statistical significance: $p<0.05$.

4. Discussion

Managing and treating poor ovarian responders are still matter of debate in the field of IVF 1, 2. Although there have been many strategies suggested in the management of poor responder patients, there is no consensus on most beneficial approach. In our study, we aimed to demonstrate whether the use of letrozole with gonadotropins has any additional beneficial effects on IVF outcomes when compared to single use of gonadotropins among patients who were classified as POSEIDON groups 3 and 4.

Our study has some limitations including retrospective design and small sample size. Meanwhile, the inclusion of a relatively homogenous group of only POSEIDON group 3 and 4 patients and patients with only one failed cycle was its strengths. The low implantation and pregnancy rates can be explained by selecting patients who were classified as POSEİDON group 3 and 4 and already who had failed IVF cycles due to several reasons.

Management of patients with low ovarian reserve is still controversial. It has been recommended that adding letrozole to gonadotropins in GnRH-a cycle in patients with low ovarian reserve may have beneficial effects 5-10. Goswami et al. published the first article in literature which showed the effectiveness of letrozole in IVF treatment in patients with low ovarian reserve and concluded that adding 2.5 mg letrozole to r-FSH significantly decreased the cost of IVF cycle due to use of lower gonadotropin doses 7.

To the extent of our understanding, the only study similar to our findings was published by Ozmen et al. Similar to our investigation, in the LzGA group, the mean total dose of rFSH and serum estradiol concentrations on the day of human chorionic gonadotrophin administration were notably lower. Their findings indicated that the supplemental utilization of letrozole appeared to enhance IVF cycles by reduction cycle cancellation rate and to decrease the cost by lowering the overall gonadotropin dose required [8].

We found cancellation rates to be similar in both groups in contrast with this study. Similar with recent studies, we found that patients with poor prognosis had less need for gonadotropins and GnRH antagonists in the letrozole-added group in agreement with the studies investigating effectiveness of letrozole in patients with low ovarian reserve [7, 8, 17]. Therefore, adding aromatase inhibitors to treatment protocols of low responders seems cost-effective.

Table 3: Cycle outcomes between groups.

Variables	LzGA Group (N=58)	GA Group (N=40)	*p*-Value
Follicles >14mm on hCG day	3.34±2.53	3.13±1.89	0.64
Follicles >17mm on hCG day	1.97±1.46	1.95±1.33	0.95
Total follicles	5.57±3.22	5.73±3.11	0.81
Top-quality embryos	0.78±0.87	1.15±1.33	0.97
Day of embryo transfer	2.10±1.68	2.50±1.82	0.27
M2 oocytes	2.71±1.80	2.58±1.72	0.71
Retrieved oocytes	3.17±2.12	3.20±2.27	0.95
M2 oosit ratio	89.76±19.32	81.78±22.76	0.06
2PN zygotes	1.90±1.63	1.90±1.72	0.99
Fertilisation ratio	65.99 ± 37.25	66.58 ± 37.02	0.93
Implantation ratio	22.09 ± 38.27	22.41 ± 39.15	0.97
No of transferred embryos	0.98 ± 0.76	1.13 ± 0.82	0.38
Embryo transferred cycles rate	70.67 (41/58)	72.50 (29/40)	0.84
Cycle cancelation rate	29.33 (17/58)	27.50 (11/40)	0.84
Day 2 transfer	10	5	0.86
Day 3 transfer	24	15	0.52
Day 5 transfer	7	9	0.17

Mean ±SD (range) or percentage (number/total). LzGA=letrozole plus gonadotropins. GA=gonadotropins only. Statistical significance: $p<0.05$.

Table 4: The causes of cycle cancelation for each cycle.

	Fertilisation Failure	Development Failure	No Oocytes	Morphologic Problem	Abnormal fertilisation	Degenerated oocytes	Total
Previous cycle of the trial group Gonadotropins only	10	5	7	6	1	1	30
Gonadotropins+letrozol Antagonist cycle	5	7	2	1	1	1	17
Previous cycle of the control group Gonadotropins only	3	6	1	2	2	0	14
Gonadotropins only Antagonist cycle	5	5	0	1	0	0	11
Total	23	23	10	10	4	2	72

Table 5: Pregnancy results.

Cycles	Chemical pregnancy positive %	Clinical pregnancy positive %	Live Birth positive %
Previous cycle of the trial group (Gonadotropins only)	5 (3/58)	3(2/58)	0(0/58)
LzGA Group	20.7 (12/58)	15.5(9/58)	10.3(6/58)
Previous cycle of the control group (Gonadotropins only)	15(6/40)	10(4/40)	0(0/40)
GA Group	22.5(9/40)	20(8/40)	10(4/40)

Percentage (number/total). Statistical significance: $p<0.04$ (Chi-square test). There were no statistically significant differences between the two groups. (*p*for chemical pregnancy: 0.83, clinical pregnancy: 0.56, and live birth:0.47).

On the other hand, Garcia-Velasco et al. revealed the efficacy of letrozole co-administration. In contrast to our study, 2.5 mg letrozole given in the first 5 days of stimulation in the high-dose FSH/hMG, GnRH-a protocol resulted in a higher number of oocytes retrieved and increased implantation rate[6]. Unfortunately, such promising results have not been obtained in subsequent randomized controlled trials. In an another study with Moini et al., the total oocyte counts and MII oocyte number were statistically significantly higher in the letrozole group. However, there was no difference in implantation, fertilization, and pregnancy rates[11]. Shapiro et al. concluded that, MII oocytes, 2PN embryos, and good quality embryos were significantly higher in gonadotropin-letrozole cycles [5]. Similarly, in our study, the ratio of MII oocyte was found to be higher in the letrozole group.

Yan Lee et al. found that the letrozole group used a significantly lower dose of HMG than the controls and the HMG duration was significantly shorter. Although less were oocytes collected in the letrozole group, the number of transferred oocytes was similar. In contrast to our study, they reported that the duration of the GnRH-antagonist treatment was similar in both groups. Similar to our study; cancellation rate, implantation rate, ongoing pregnancy rate, live birth rate, and cumulative live birth rate were comparable for both groups [20]. However, other studies did not find any positive effect of letrozole and the results of the available studies are conflicting [4, 13, 16, 17]. In our study, adding letrozole to the treatment did not change the results statistically.

5. Conclusions

As a result, we found that addition letrozole to gonadotropins during early follicular phase to GA protocol did not have a contribution to pregnancy outcomes. However, a significant reduction in the GnRH antagonist dose and a significantly higher progesterone level at hCG day was detected. There was no difference between the groups in terms of chemical, clinical pregnancy and live birth rates.

Limitations of the Study

The main limitation in present study is the relatively smaller sample size.

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Conflict of Interests

Authors declare no conflict of interest. All authors read and approved final manuscript.

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Author Contributions

CK; Design: CK, AD, EŞG; Supervision: AD, EŞG; Data Collection and/or Processing: KK; Analysis and/or Interpretation: CK, KK; Literature Review: CK, KK; Writing: CK; Critical Review: AD, EŞG**.**

Ethical Approval

The study was approved by the University of Health Sciences Research Ethics Committee (Protocol Number: 2022/07-14, Date: 18.07.2022).

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author

Consent to participate

Consent was obtained from the all patients participating in the study.

Informed Statement

The all patients who agreed to participate in the study signed the informed consent form.

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Comparison of the Postoperative Analgesia Effects of Patient-Controlled Analgesia and Epidural Catheter After Posterior Instrumentation Surgery

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Abstract: To prospectively assess the effects of intravenous patient-controlled analgesia (IV PCA) and epidural patient-controlled analgesia (epidural PCA) on postoperative pain management following posterior instrumentation surgery. The study involved the ASA 1-2 group, 60 patients who underwent elective thoracic or lumbar posterior instrumentation surgery at our tertiary centre for spinal stenosis. Two groups of patients were created: Group 1 (n=30), IV PCA group, and Group 2 (n=30), epidural PCA group. IV PCA was applied by fentanyl. Epidural PCA was maintained by lading to epidural space by the neurosurgeon. Bupivacaine was administered to Group 2 patients in the recovery room. Following surgery, patients in both groups were assessed for pain using the visual analogue scale (VAS) and for motor block using the Bromage scale. Additionally, hemodynamic parameters, side effects, and patient satisfaction were noted. Following 48 hours, patients' overall rescue analgesia, opioid, and local anaesthetic requirements were recorded. Postoperative VAS scores of Group 2 at the 1st, 2nd, 4th, 8th, and 16th hours were lower than Group 1 and these differences was statistically significant. Postoperative patient satisfaction scores at 1st, 2nd, 4th, 8th, 12th, 16th, 20th, 24th, 30th, 36th, 42nd, and 48th hours were significantly different between the groups and the patient satisfaction scores of Group 2 were higher than the Group 1. Side effects were similar in both groups. Group 1 required statistically significantly higher number of rescue analgesia. This study shows that epidural PCA is more comfortable than IV PCA with low VAS and high patient satisfaction scores. As a conclusion, epidural PCA is a safe, highly efficient method for patients with posterior instrumentation surgery. ©2023 NTMS.

Keywords: Analgesia; Patient-Controlled; Pain; Postoperative.

1. Introduction

Posterior instrumentation surgery is a successful treatment for spinal stenosis [1]. Postoperative pain, however, is a usual and a serious incident after posterior instrumentation surgery. Poorly controlled postoperative pain not only reduces patients' quality of life and satisfaction, but also increases hospitalization, cardiopulmonary complications, pain-related morbidity, and hospital mortality [2-4]. However, there is no consensus on postoperative pain management after posterior instrumentation surgery [4, 6, 7].

Intravenously administered systemic opioids are often used for pain control, but several dose-related complications associated with opioid use have been reported. Anaesthesiologists should make all efforts to decrease the quantity of opioid supplied and discover alternative medications or ways for pain control

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because posterior instrumentation surgery is typically performed on elderly individuals [5].

Effective postoperative pain management techniques include the use of opioids or epidural analgesia along with local anaesthesia. Compared to intravenous PCA, these methods have certain advantages in that they offer more effective pain control and cause fewer complications during stomach, thoracic, and spine operations. The effectiveness and safety of continuous epidural analgesia with fentanyl, intravenous PCA, and bupivacaine for posterior instrumentation surgery, particularly postoperative complications, have not been demonstrated, however [6, 7]. In a prospective randomized controlled trial, we sought to compare the clinical outcomes of intravenous PCA with epidural analgesia.

2. Material and Methods

The study was approved by Atatürk University Faculty of Medicine Ethics Committee (06.06.2013(5)/4). Patients who willingly participated in the study and gave their informed consent. In this study CONSORT (Consolidated Standards of Reporting Trails) reporting guideline was used.

2.1. Patients

Sixty cases of ASA 1-2 group (18-65-year-old), who underwent elective thoracic or lumbar posterior instrumentation surgery for spinal stenosis at our tertiary centre were enrolled prospectively (Figure 1). According to the patients' preferences, they were split into two groups (Group 1; IV PCA group; Group 2; epidural PCA group).

Exclusion criteria included having a known allergy to study drugs, having undergone surgery at the fourth or higher level, refusing to participate in the study, using drugs previously, being pregnant, having a heart arrhythmia, or having a neurological deficiency.

2.2. Anaesthesia Method

For the induction of anaesthesia in two groups, IV 2 mg/kg propofol, 2 μg/kg fentanyl, 1 mg/kg lidocaine and 1 mg/kg rocuronium were administered. Anaesthesia was continued with 1-3% sevoflurane in 45% O_2+55% N_2O.

Group 1 (IV PCA Group): In Group 1 patients, PCA device in the recovery room was set as 75 μg loading, 20 μg/hour basal infusion, 20 μg bolus, 10 minutes locked time, fentanyl at a concentration of 10 μg/mL. If the VAS scores were above 3, 30 μg fentanyl bolus was performed for rescue analgesia and the subsequent bolus doses were increased to 30 μg. 75 mg of diclofenac sodium IM total amount of opioid was recorded after 48 hours of cases and rescue analgesic count.

Group 2 (Epidural PCA Group): For Group 2, still epidural space is open, the neurosurgeon placed the epidural catheter via the intact skin by the Tuohy needle at the end of the operation (Figure 2). In the recovery room, 0.1% bupivacaine+2 μg/mL fentanyl mixture was prepared and the PCA device was set as 10 mL loading dose, 10 mL/hour basal infusion, 10 mL bolus and 45 minutes locked time. If the VAS scores were above 3, 20 mL bolus dose was done for the rescue analgesia. In case of no analgesia within 20 minutes, the concentration of local anaesthetic was increased to 0.125% bupivacaine+2 μg/mL fentanyl and 20 mL bolus dose was performed.

2.3. Rescue Analgesia

If the pain still does not occur within 20 minutes, then 75 mg diclofenac sodium IM done. At the end of 48 hours, total opioid, local anaesthetic amount, and rescue analgesia count were recorded.

2.4. Measurements and Side Effects:

patients in both groups were assessed for pain using the visual analogue scale (VAS) and motor block using the Bromage scale at the 1^{th}, 2^{nd}, 4^{th}, 8^{th}, 12^{th}, 16^{th}, 20^{th}, 24^{th}, 30^{th}, 36^{th}, 42^{nd}, and 48^{th} hours following surgery, Simultaneously, hemodynamic parameters, and patient satisfaction (0=bad, 1=moderate, 2=good, 3=very good, 4=excellent) were recorded. The side effects such as nausea, vomiting, and itching were evaluated and recorded.

2.5. Statistical Analyses:

The statistical calculations were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY). Continuous variables are expressed as Mean±Standard Deviation (SD), categorical data are expressed as n (%). According to the Power analysis, it has been calculated that a minimum of 21 patients should be evaluated for 0.05 error and 80% power *(http://clincalc.com/stats/samplesize.aspx)*. Histogram, Shapiro-Wilk and the one-sample Kolmogorov-Smirnov test were performed to determine the distribution of the data. Independent sample t-test was used to compare demographic characteristics, operation times, systolic, diastolic blood pressure values, pulse variables, VAS values and patient satisfaction scores in both groups. Linear regression analysis was performed to determine the effect of systolic, diastolic blood pressure values and pulse variables on VAS scores and patient satisfaction in each group. Chi-square test was used for side effect analysis. All tests were applied as two-sided whereby p-value <0.05 was considered as statistically significant.

3. Results

Demographic features of the groups are seen at Table 1. There was no statistically significant difference between the groups in terms of age, weight and gender. The operation time of the cases was similar in both groups.

VAS scores in Group 2 at postoperative 1^{st}, 2^{nd}, 4^{th}, 8^{th}, and 16^{th} hours were significantly lower than those in Group 1 (Table 2).

The patient satisfaction scores were higher in Group 2 than Group 1 for postoperative 1st, 2nd, 4th, 8th, 12th, 16th, 20th, 24th, 30th, 36th, 42nd, and 48th hours and the differences were statistically significant (Table 3).

In Group 1, 16 cases and in Group 2, 4 patients received rescue analgesia as 75 mg diclofenac sodium IM done. In Group 2, the need for rescue analgesia was found to be lower than group 1 and the differences was statistically significant (Table 4).

None of the 60 patients in Group 1 and Group 2 had urinary retention, urinary incontinence, or motor block during their hospitalization. All patients' Bromage scale was 0. Nausea and vomiting were seen in 4 cases in Group 1, 3 cases in Group 2, and metoclopramide intervention was performed.

Table 1: Demographic features of the groups.

	Group 1 (n=30)	**Group 2 (n=30)**	**P Values**
Age	51.5±11.2	53.3±8.7	0.483
Weight	75.6±13.1	79.7±12.3	0.226
Sex	16(53%)/14(47%)	15(50%)/15(50%)	0.800

All values are given as Mean±SD. Gender is given in %. P<0.05: statistically significant (independent samples t-test).

Table 2: Postoperative VAS Scores.

Time	**Group 1 (n=30)**	**Group 2 (n=30)**	**P Values**
1st hour	7.70±0.87	6.93±1.28	0.009
2nd hour	5.00±1.20	2.87±0.73	0.000
4th hour	3.03±0.85	2.00±0.37	0.000
8th hour	2.10±0.84	1.47±0.50	0.001
12th hour	1.50±0.77	1.20±0.61	0.102
16th hour	1.37±0.76	0.93±0.69	0.025
20th hour	1.03±0.76	0.80±0.61	0.197
24th hour	0.67±0.71	0.47±0.62	0.253
30th hour	0.57±0.62	0.33±0.66	0.166
36th hour	0.43±0.62	0.20±0.48	0.122
42nd hour	0.37±0.55	0.20±0.48	0.221
48th hour	0.37±0.55	0.20±0.48	0.221

All values are given as Mean±SD. P<0.05: statistically significant (independent samples t-test).

Table 3: Patient satisfaction scores.

Time	**Group 1 (n=30)**	**Group 2 (n=30)**	**P Values**
1st hour	0.97±0.76	1.50±0.63	0.005
2nd hour	1.40±0.89	2.67±0.71	0.000
4th hour	2.30±0.65	3.23±0.77	0.000
8th hour	2.63±0.85	3.60±0.56	0.000
12th hour	2.97±0.80	3.67±0.54	0.000
16th hour	3.17±0.69	3.80±0.40	0.000
20th hour	3.27±0.69	3.87±0.34	0.000
24th hour	3.47±0.57	3.87±0.34	0.002
30th hour	3.53±0.50	3.90±0.30	0.001
36th hour	3.53±0.50	3.87±0.43	0.008
42nd hour	3.60±0.49	3.90±0.30	0.007
48th hour	3.60±0.49	3.90±0.30	0.007

All values are given as Mean±SD. P<0.05: statistically significant (linear regression analysis).

Table 4: Rescue analgesia need.

	Group 1 (n=30)	Group 2 (n=30)	P Value
Cases	16	4	0.003

P<0.05: Statistically significant (Chi-square test).

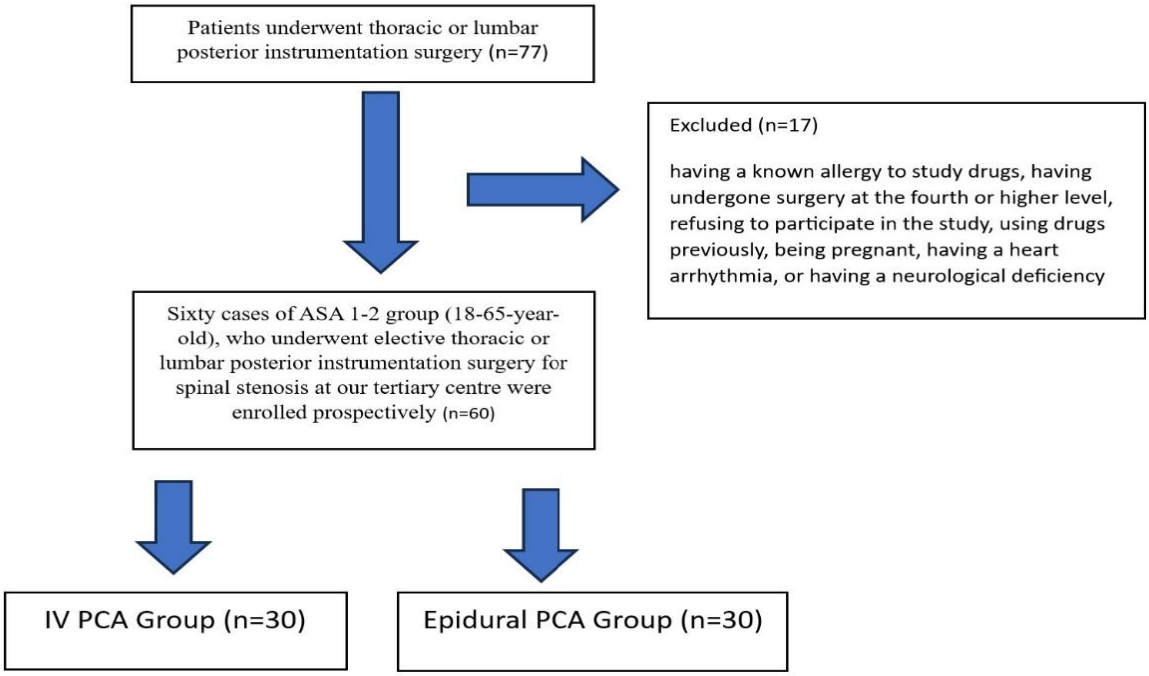

Figure 1: Flowchart of the study.

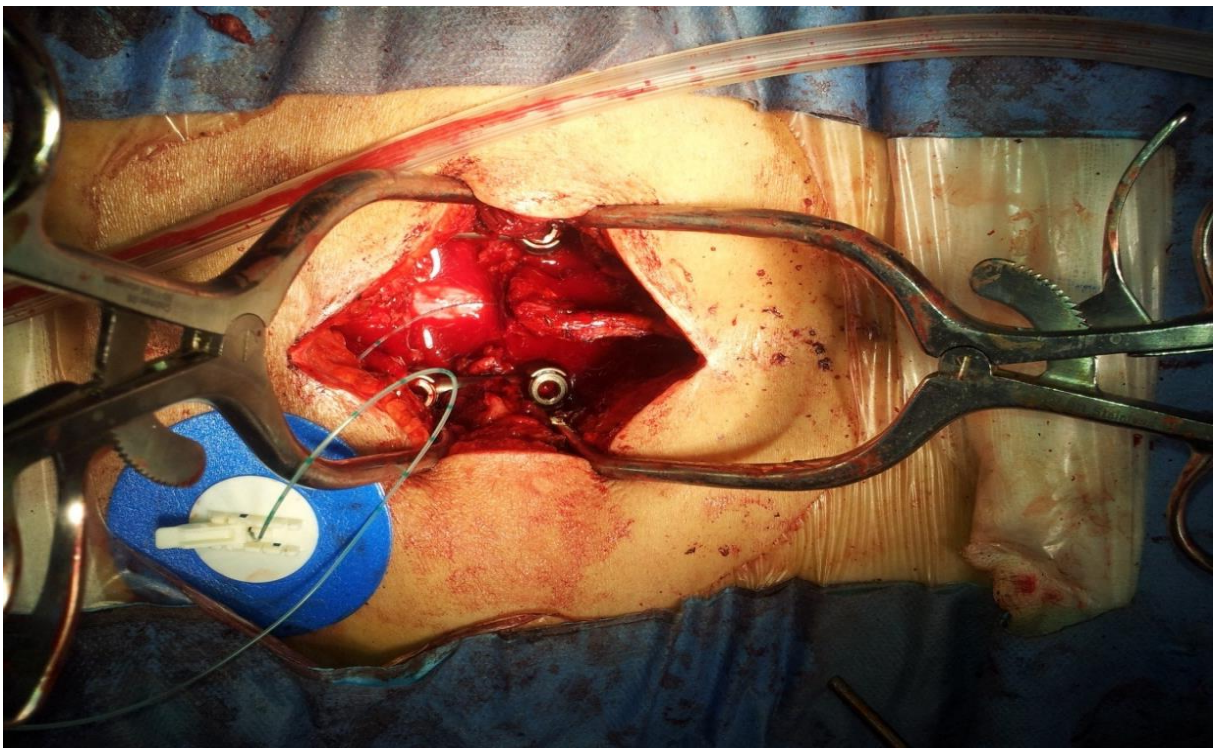

Figure 2: Epidural catheter on the epidural space.

4. Discussion

Our study found that, epidural PCA is linked with a lower pain score, more satisfied patients, and fewer complications in contrast to IV PCA in the postoperative period after thoracic and lumbar instrumentation surgery.

There are numerous views that use opioid analgesics with local anaesthesia to provide an effective analgesia method, reduce the dose of drugs to be administered, reduce the side effects of drugs, and prevent adverse physiological effects from endocrine stress response and painful stimulation [8,9]. Acute opioid-associated respiratory depression, heart toxicity, and central nervous system depression are more likely with epidural or intrathecal opioids. Since older people are typically candidates for posterior instrumentation surgery, adverse effects from epidural opioids may be more common and severe. Although continuous infusion of epidural opioids appears to be more prone to side effects, single-dose epidural opioids may be insufficient to control postoperative pain [8-10].

Most patients with posterior instrumentation surgery have severe pain. Epidural PCA and IV-PCA are two common options in the treatment of postoperative pain. In studies, different drug regimens have been compared at different doses but there is no universally accepted consensus about which analgesic approach performs better [7]. The literature has different opinions on the efficiency and safety of epidural pain control techniques. It was discovered that there is no discernible difference between those receiving epidural analgesia and those receiving a placebo. However, paraesthesia was more common in the epidural group [12]. Additionally, a different study discovered no discernible difference between IV PCA and epidural PCA. Only the intestinal sounds were reported earlier in the epidural group [13]. A study conducted on three groups of patients undergoing scoliosis surgery stated that the double catheter used for postoperative analgesia was superior to both a single catheter and iv PCA [14]. A case-control study consisting of 120 patients with lumbar degenerative disease has demonstrated, in the epidural PCA group, significantly lower VAS scores were detected in 3rd, 6th, 12th, 24th and 48th hours of surgery-related pain compared to the iv PCA group. In addition, the level of patient satisfaction was significantly higher than the PCA group and the side effects were lower [15].

Motor block after spinal cord surgery is an important issue that concerns all aspects of postoperative care. Close observation is necessary as higher concentration and infusion rate may cause temporary motor block. A study with 72 patients undergoing major spinal surgery, epidural PCA with ropivacaine and sufentanyl was compared to IV PCA with morphine. The excellent pain control in this study was probably due to a higher concentration of ropivacaine, a higher infusion rate, and the use of epidural opioids. In this study, ropivacaine was prepared at a concentration of 0.125% and this resulted in motor block in 5 of 28 patients [6]. In another study, the use of ropivacaine, which was %0.1, provided the desired pain control, but in nine of the 29 patients, unwanted transient loss of sensation and motor block were seen [16]. Since we utilized 0.125% bupivacaine in our trial, none of the patients experienced motor block. In addition, there are publications suggesting that the use of drugs at low concentration or low volume will result in failure [17, 18]. During an observational study of fourteen patients underwent posterior spinal fusion surgery, the epidural catheter was placed by the surgeon and checked by X-ray using radiopaque material. In 7 patients with high VAS scores, the epidural catheter was not in the proper position. It suggested that the correctly placed surgical epidural catheters could provide better postoperative analgesia and misplaced catheters were associated with inadequate analgesia [19]. In another study, 24 hours after spinal fusion surgery, in 33 (8%) of 413 patients, epidural infusion was stopped due to severe pain, this was stated to be brought on by the epidural catheter being positioned incorrectly. According to these results, insufficient analgesia after spinal surgery may be due to the epidural catheter's improper placement, which in turn leads to insufficient drug infusion into the epidural area [20]. In addition, bleeding in the surgical area or drainage catheters applied to this area may also be the cause of inadequate infusion.

The surgeons in our study placed the epidural catheter under direct visualization without radiographic validation. Patients were also classified according to their choices after the procedure was described. These may be the limitations of our study.

5. Conclusions

In conclusion, epidural PCA is a safe, highly efficient method for patients with posterior instrumentation surgery by providing effective postoperative analgesia, no serious side effects, high patient satisfaction.

Limitations of the Study

Additional to above mentioned limitations there were potential population bias, limited number of patients, single centre study.

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None.

Conflict of Interests

The authors declare no conflict of interest.

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Author Contributions

MAK, HAA: Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing-original draft preparation, writing-review and editing, visualization, and supervision. All authors have read and agreed to the published version of the manuscript.

Ethical Approval

It was approved by Atatürk University Faculty of Medicine Ethics Committee (06.06.2013(5)/4).

Data sharing statement

Available upon request from the corresponding authors. The data are not publicly available due to compliance with privacy laws.

Consent to participate and Informed Statement

Adults who willingly participated in the study and gave their informed consent to be study subjects provided all the data.

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Early Recurrence of Lumbar Disc Herniation: A Retrospective Analysis of the Role of Discectomy Volume and Other Influencing Factors

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Abstract: The aim of this study is to conduct a detailed examination of cases of "early recurrence" encountered following lumbar disc herniation surgery and to compare the data obtained with findings in the existing literature. This retrospective study analyzed the data of 856 patients who underwent surgery for recurrent lumbar hernia at our hospital between 2012 and 2022. We expanded the definition of "early relapse" in the literature to set inclusion and exclusion criteria, resulting in a cohort of 43 patients who met these criteria being included in the study. We assessed the severity of symptoms based on patients' Visual Analog Scale (VAS) scores at baseline and during subsequent periods. Patients requiring reoperation within the first 12 months were divided into two main groups: those undergoing reoperation within the first 6 months and those undergoing reoperation between 6-12 months. However, we found no statistically significant difference between the two groups regarding age, gender, comorbidities, and other determinants. Notably, patients undergoing surgery within the first 3 months were observed to be of advanced age. Comparing the data from our analysis of patients with "early recurrent lumbar disc herniation" to findings in the literature, we noted that similar variables were not significant in our series. An interesting observation was that both full endoscopic and microscopic methods yielded similar early recurrence rates. This finding is particularly noteworthy because full endoscopic discectomy often involves sequestrectomy, and the volume of the disc removed is typically minimal. Hence, our study suggests that the volume of the disc removed during surgery may not be as influential in the development of early recurrence as previously thought. These findings provide an important foundation for future research. ©2023 NTMS.

Keywords: Lumbar Discectomy; Recurrence; Early Recurrence; Microscopic Discectomy.

1. Introduction

Low back pain is one of the most commonly encountered pain symptoms in the general population. Lumbar Disc Herniation (LDH) frequently causes both low back and leg pain. In cases of symptomatic lumbar disc herniations where radicular pain is unresponsive to medical treatment and there is radiological evidence consistent with LDH pathology, surgical intervention is indicated [1-3]. Progressive neurological deficits, cauda equina syndrome, and severe radicular pain are cited as dications for emergency LDH intervention in the

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literatüre [2, 3].

The primary objective of LDH surgery is to alleviate pressure on neural tissues and prevent the progression of neurological symptoms, with the alleviation of pain symptoms considered a secondary benefit. A "recurrence" is evaluated as the return of neural compression at the same level and side as previously treated, accompanied by a corresponding return of pain symptoms post-surgery [4, 5]. In the past, "recurrence" was used to describe the resumption of pain following a six-month pain-free period post-LDH surgery [6, 7]. However, recent studies- facilitated by more frequent and easily accessible MRI imaging and improved patient access to healthcare centers-have questioned the necessity of a six-month well-being period for defining recurrence. Some now categorize a lumbar disc herniation at the same level and side requiring new surgery within 12 months post-initial operation as "early recurrence" [9-11]. Publications emphasizing the concept of "early recurrence" predominantly share results of Full Endoscopic Lumbar Discectomy (FELD) methods for lumbar discectomy [12-14].

Our study aims to examine our recurrence rates within the first 12 months, a period considered early according to the literature. We plan to evaluate "early recurrence" patients based on occurrences within the first six months and those between six and twelve months, aligning with the approaches found in existing research. Furthermore, we introduce the concept of "very early recurrence," not yet present in the existing literature, to assess the characteristics of patients experiencing recurrence during the first one to three months post-operation.

2. Material and Methods

Our study entailed a retrospective analysis of patient records and imaging studies archived in our hospital. We assessed the clinical information and imaging results of 856 patients who underwent surgery for recurrent lumbar disc herniation between 2011 and 2022 in our clinic. Among these, we scrutinized those who underwent reoperation within 12 months following their initial surgery. We analyzed the characteristics of 43 patients who met the inclusion criteria for the study. Written informed consent was secured from patients (or their legal guardians) for the sharing of diagnostic images and the publication of their medical data.

Inclusion Criteria for the Study:

*Both the initial and subsequent surgeries were performed at our hospital.

*The initial surgery targeted single-level and unilateral lumbar disc herniation (LDH).

*Flexion-extension radiographs and anteroposterior scoliosis radiographs were available from before the first surgery, showing no severe degenerative lumbar pathologies such as listhesis and scoliosis.

Pre-operative lumbar magnetic resonance imaging (MRI) results from the initial surgery were retrievable from our hospital's imaging system.

*Contrast-enhanced lumbar MRI results before the second surgery were accessible in our hospital's imaging system.

*Both pre-operative and post-operative Visual Analog Scale (VAS) scores for patients were documented in the system.

*Patients demonstrated "absolute improvement" in VAS scores during inpatient post-surgery visits and at outpatient check-ups on the 20th day following the surgery, compared to pre-operative scores.

Exclusion Criteria:

*Patients who underwent multiple recurrence surgeries.

*Patients requiring stabilization due to signs of instability observed during the second surgery.

*Patients failing to show post-operative improvement in Visual Analog Scale (VAS) scores.

*Patients who had early surgery due to complications such as lumbar epidural hematoma and cerebrospinal fluid (CSF) fistula were excluded from the study.

*Patients reporting a decline in Visual Analog Scale (VAS) scores after a minimum of 30 days of well-being post-operative improvement, and confirmed to have pressure consistent with lumbar disc herniation at the same level and side as the previous surgery in contrast-enhanced lumbar MRI upon recurrence of symptoms, were categorized as experiencing "Early Recurrence" and were incorporated into the study (Figure 1).

2.1. Statistical Evaluation

We conducted the statistical analysis utilizing SPSS 22.0 software. In descriptive statistics, we represented continuous variables using mean±standard deviation, and categorical variables using frequency and percentage. The Kolmogorov-Smirnov test facilitated the normality analysis. Owing to the non-normal distribution of numerical variables, we employed the Mann-Whitney U test for the analysis. We acknowledged a p-value of <0.05 as indicative of statistical significance.

3. Results

In our study, a total of 43 patients were included. The average age of the participants was 49.93±10.87, ranging from 28 to 76 years. Out of these, 23 patients (53.5%) were female, and an equal number reported no comorbidities. Furthermore, 11 patients (25.5%) had hypertension (HT), and 9 (20.9%) had diabetes mellitus (DM). Other comorbidities included both HT and DM in three patients (6.9%), coronary artery disease (CAD) in two (4.6%), and chronic obstructive pulmonary disease (COPD) in one (2.3%). Due to the low frequency of the latter conditions, the statistical evaluation of comorbidities focused on HT and DM.

The average body mass index (BMI) was 30.44±3.78, with a span of 21-40. When assessing the recurrent LDH levels, 28 patients (65.1%) had it at the L4-L5 level, 12 patients (27.9%) at the L5-S1 level, and 3 patients (7.1%) at the L3-L4 level. Over half, 22 patients (51.2%), had the herniation on the right side.

Recurrence was assessed based on VAS (Visual Analog Scale) scores. Any patient not showing an improvement in VAS scores during the initial 20-day follow-up was not deemed to have "recurrence." The patients' average preoperative VAS score was 8.5 (range: 6-10), which dropped to 2 (range: 1-3) 24 hours post-operation, and further decreased to 1.25 (range: 0-2) during outpatient follow-up. When symptoms resumed, the evaluated VAS score was 6.61 (range: 5-8).

Patients exhibiting symptoms of recurrence as evidenced by contrast-enhanced lumbar MRI findings underwent another surgery. These individuals were then classified as having early recurrence within the first 12 months according to the recurrence surgery date. Subsequently, we divided these 43 patients into two groups: those undergoing a second surgery between the 1st and 6th month postoperatively (41.8%, group 1) and those having it between the 6th and 12th month (58.1%, group 2). We assessed patient variables accordingly (Table 1).

During the assessment, it was noted that 4 patients (9.3%) had undergone surgery within the initial three months. We labeled this category as "very early recurrence" and separately evaluated these individuals from others experiencing recurrence between months 3 and 12 (Table 2).

Regarding the initial surgery, 18 patients (41.8%) had the operation within the first 6 months, while 25 patients (58.1%) underwent surgery between the 6th and 12th month. Specifically, 4 individuals (22.2%) from the first group had surgery within the first 3 months. We observed that the mean disc volume removed during the initial surgery was 19.51±5.54 cc (range: 10-35) in the first group and 19.07±5.14 cc (range: 10-30) in the second group.

Comparative analysis of the variables between the two groups revealed no significant correlation with age, gender, comorbidities such as HT and DM deemed significant in recurrent disc literature, herniation localization, or the volume of the removed disc (Table 1).

In analyzing patients undergoing reoperation due to recurrence within the first three months as a distinct group, we found that only their higher average age bore statistical significance (Table 2)

Table 1: Analysis of Demographic Characteristics of Patients Requiring Repeat Surgery Within 6 Months (Group 1) and Between 6-12 Months (Group 2) After the Initial Surgery.

	Grup 1 (n=18)	**Grup 2(n=25)**	**P Value**
Average Age	50 (42-57)	53(37.25-58.25)	0.856**
Gender			
Women	4 (17.3%)	19 (82.6%)	
Men	14(70%)	6 (30%)	0.323*
Bmi	30 (28-33)	30.5(30-31.75)	0.888**
Comorbidity			
Yes	8 (40%)	12 (60%)	0.261*
No	10 (43.4%)	13 (56.5%)	
HT			
Yes	1(0.09%)	10 (90.9%)	0.331*
No	17(43.7%)	15(46.8%)	
DM			
Yes	3(33.3%)	6(66.6)	0.368*
No	17 (50%)	17 (50%)	
Lumbar Level			
L3-L4	3 (100%)	0	
L4-L5	10(35.7%)	18(64.2%)	0.161**
L5-S1	5(41.6%)	7 (58.3%)	
Disc Volume Excessed	20(15-20)	22.5(20-25)	0.167**

* Pearson Chi-Square ,**Mann-Whitney-U test

Table 2: Comparison of Patients Requiring Recurrence Within 3 Months After the Initial Surgery with Others.

Recurrent surgery in the first 3 months	**YES (n=4)**	**NO (n=39)**	**P VALUE**
Average Age	65(47.5-73.5)	50(41-56)	**0.049****
Gender			
Women	2(8.7%)	21 (91.3%)	
Men	2(10%)	18(90%)	0.641*
Bmi	30.5(28.25-32.75)	30(28-33)	0.920**
Comorbidity			
Yes	3(15%)	17(85%)	0.323*
No	1(4.3%)	22(95.7%)	
Ht			
Yes	1(12.5%)	7(87.5%)	0.576*
No	3(8.6%)	32(91.4%)	
Dm			
Yes	3(42.9%)	4(57.1%)	0.261*
No	1(2.8%)	35(97.2%)	
Lumbar level			
L3-l4	3(%100)	0	0.135*
L4-l5	0	28(%100)	
L5-s1	1(%8,3)	11(%91,6)	
Disc volume excessed	17.5(15-31.25)	20(15-25)	0.984**

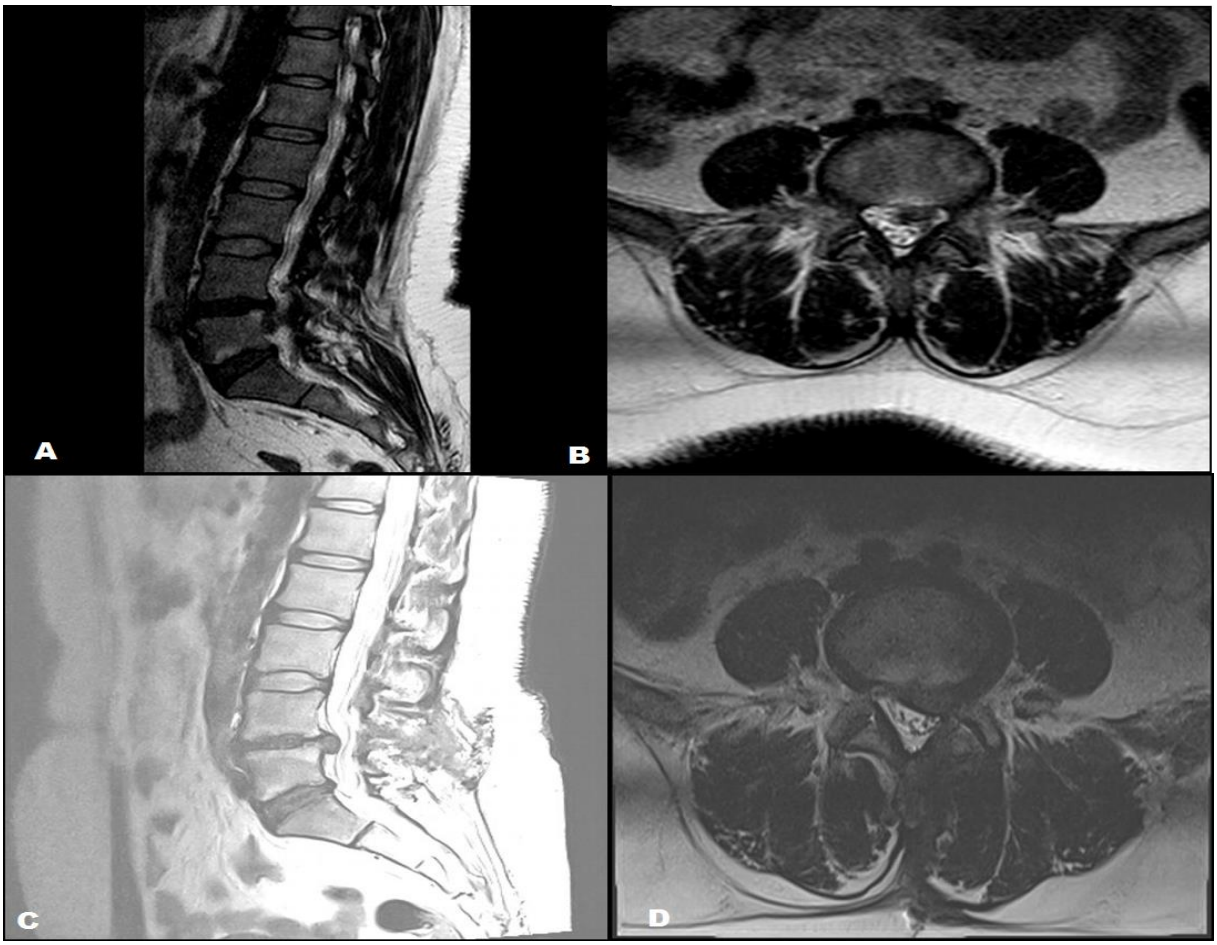

Figure 1: A 35-year-old female patient presented with lower back and left leg radicular pain consistent with left L4-5 lumbar disc herniation (LDH) pathology. 1A - Sagittal T2-weighted image showing downward-migrated LDH view. 1B - Axial T2-weighted image displaying compression on the left L5 nerve root. The patient underwent lumbar discectomy surgery, resulting in a decrease in VAS score from 8 to 1. However, in the eighth month after the surgery, her pain resumed in a similar manner, with a VAS score of 9.1C-D - A subsequent MRI revealed recurrent disc pathology at the same level and side, without contrast enhancement. The patient underwent recurrent LDH surgery, leading to a VAS score improvement to 2. Patient data were obtained from our medical records and MRI, and she was included in the study as a participant in "Group 2."

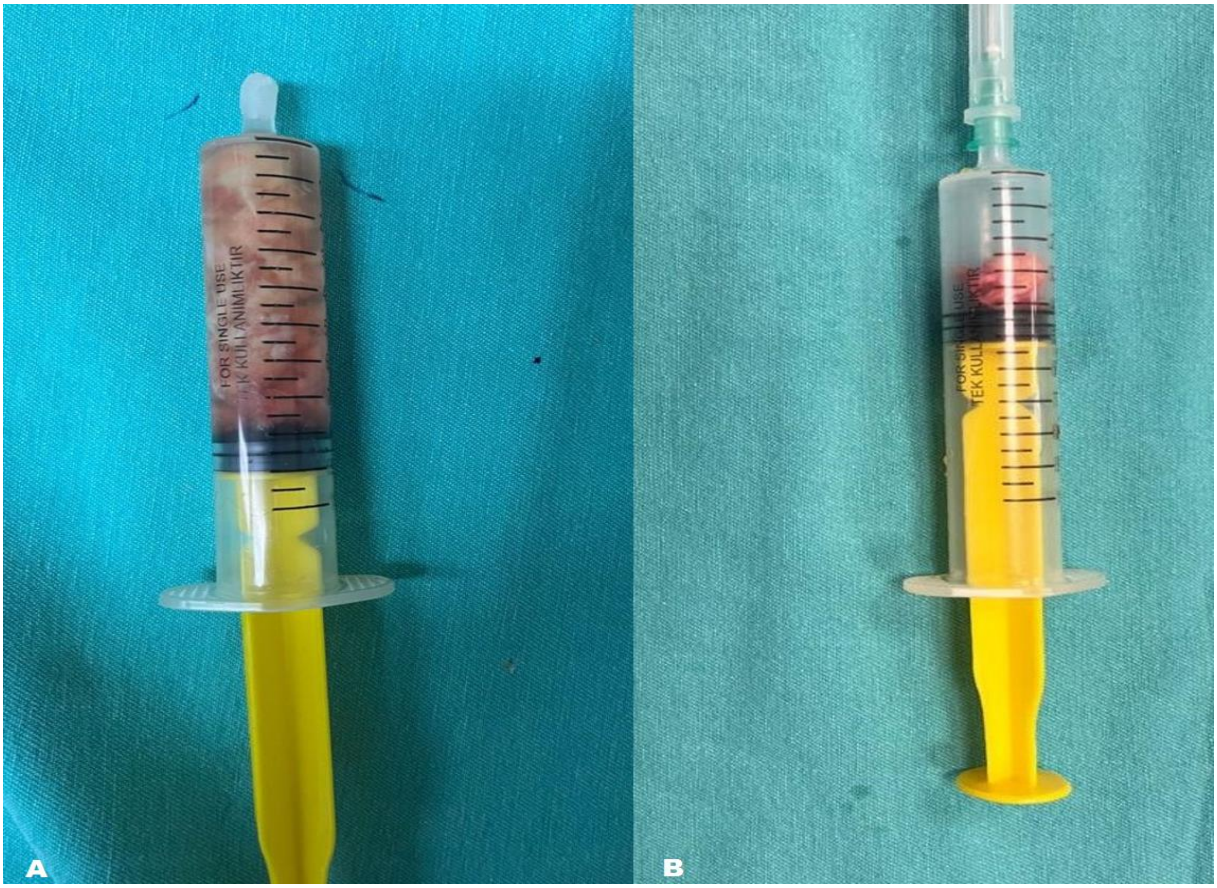

Figure 2: An illustrative depiction of a common practice in our clinic and many neurosurgery departments, involving volume calculation through the accumulation of excised discs using syringes during surgery. 2A - Visual representation of the average volume of extracted discs after microdiscectomy surgery (10-35 cc). 2B - Visual representation of the volume of excised discs using the sequestrectomy method, more commonly preferred in full endoscopic surgeries (1-3 cc).

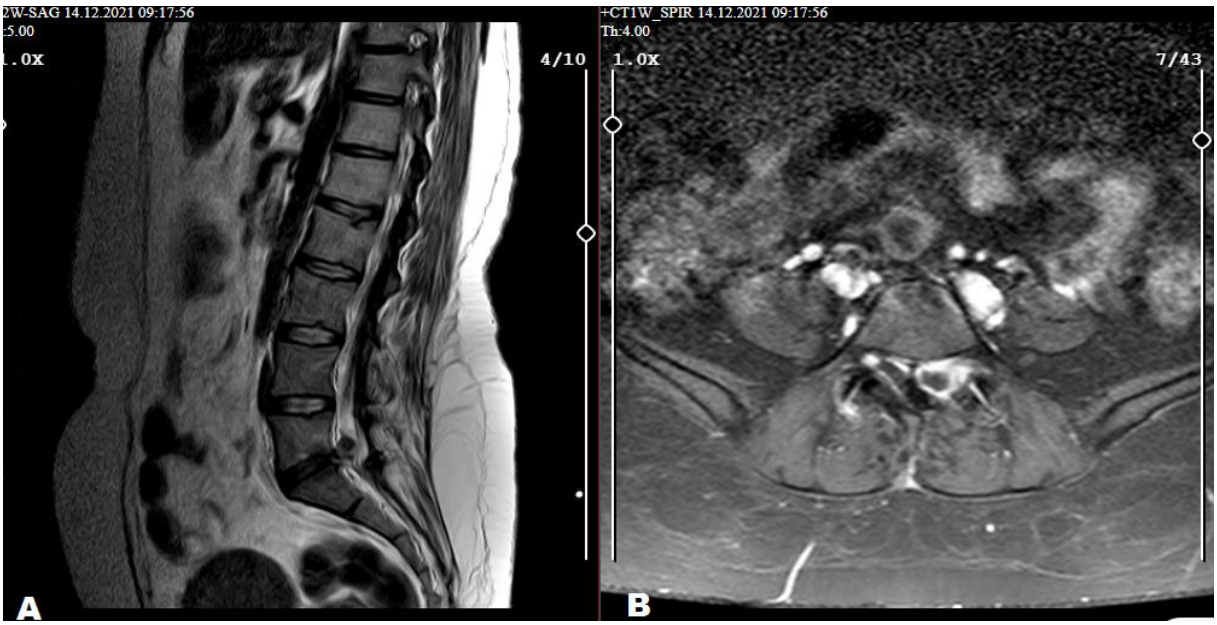

Figure 3: Evaluation of a patient who reported the re-emergence of pain 32 days after the initial surgery using contrast-enhanced lumbar MRI. 3A - Sagittal T2-weighted image demonstrating upward-migrated disc pathology and compression on neural tissues. 3B - Axial contrast-enhanced T1-weighted image showing neural compression and an early contrast-enhancing lesion. Although the radiology report initially interpreted the findings in favor of scar tissue, a second surgery was performed due to compression. Postoperatively, the VAS score improved to 1. The patient was included in the study as a participant in "Group 1."

4. Discussion

In our study, we evaluated 43 patients who underwent recurrent surgery between 1-12 months post-surgery from a pool of 856 patients treated in our clinic from 2011 to 2022. Consequently, we identified our early recurrence rate as 5%. This rate aligns with the general recurrence rates cited in the existing literature, which range between 5-15% [1-3]. Hence, our clinic's recurrence rates are consistent with those documented in the literature.

Traditionally, studies analyzing early recurrence in Lumbar Disc Herniation (LDH) patients tend to focus on those undergoing Full Endoscopic Lumbar Discectomy (FELD). However, our research took a different route; all patients classified under "Early Recurrence" had undergone Microscopic Lumbar Discectomy (MLD). Despite this deviation, our findings align interestingly with the broader research landscape; while FELD surgeries report a 7% early recurrence rate, our MLD patient cohort exhibited a slightly lower rate of 5%. This finding is noteworthy as it indicates comparable early recurrence rates between the endoscopic and microscopic assessment routes.

In the existing literature, there are extensive series of studies evaluating the outcomes of Full Endoscopic Lumbar Discectomy (FELD) procedures in the early phases of Lumbar Disc Herniation (LDH) [1- 3, 12- 14]. A sequestrectomy is the most common method employed in FELD, during which the volume of the removed disc seldom exceeds 3 cc. The lower volume of removed disc in full endoscopic approaches often takes the blame for early recurrences; however, there is no statistical data to back this claim. In our study, all patients underwent Microscopic Lumbar Discectomy (MLD) with the average volume of the removed disc being 19.35 cc (ranging from 10 to 35 cc). Surprisingly, our early post-operative recurrence rates mirror those reported in FELD studies. This leads us to infer that early recurrence in LDH patients is not tied to the volume of the removed disc, thereby adding valuable data to the existing body of literature.

Several studies in the literature have sought to determine the volume of disc removed during LDH surgeries by analyzing pre-operative and post-operative lumbar MRI scans [10, 11, 16, 17]. In a departure from this norm, our study employed volume measurements taken during the operation, evaluating the disc material collected in a 50 cc syringe (Figure 2). This innovative method stands as a potential alternative to radiological assessments and could be embraced in forthcoming studies.

In studies examining risk factors associated with recurrent lumbar disc herniation (LDH), variables such as age, gender, and body mass index have been identified as significant contributors [3- 5, 12, 15]. In our research, we sought to determine whether these notable factors for recurrence hold significance for early recurrence as well. Contrary to findings from other publications, no factors emerged as significant in influencing early recurrent surgery in our study (Table 1). When we isolated cases categorized as 'very early recurrence'-those involving reoperation within the initial three months-only the age factor demonstrated notable variation, with older patients being more predominant (Table 2). Past literature indicates a heightened risk of recurrence for FELD cases involving pathologies between the L4-5 and L5-S1 vertebrae, especially when evaluating early recurrences [12-15]. In our dataset, the limited number of patients (n: 4) experiencing 'very early recurrence' necessitates validation through studies with larger cohorts. Despite this limitation, our study carries weight for its potential to augment other research projects, as it diverges from the prevalent trend of analyzing early recurrent LDH surgery patients in broader time frames-either within one year post initial surgery, or bifurcated into 1-6 months and 6-12 months categories. Our initial assessment aligned with this methodology. Notwithstanding, the secondary layer of our analysis, which contrasts patients undergoing early recurrent surgery within the first 3 months against those revisiting between 3-12 months, fills a gap in the current literature.

In our clinic, each LDH patient slated for surgery undergoes preliminary flexion-extension and anteroposterior scoliosis radiographic evaluations. Those exhibiting severe degenerative lumbar pathologies such as listhesis or scoliosis, alongside LDH, were excluded from the study based on these radiographs. Likewise, patients demonstrating instability during their first recurrent surgery through similar diagnostic procedures, and who subsequently underwent stabilization procedures, were also excluded. This exclusion strategy aimed to obviate potential instability among the study participants, warranting a focus on other factors pertinent to early recurrences in cases devoid of instability [9- 11]. The focal point of our study is to scrutinize the characteristics of early recurrences in the absence of instability.

Radiographic studies are critical in diagnosing recurrent lumbar disc herniation (LDH). However, it's important to note whether they are being used to actually diagnose recurrence or to rule out other pathologies. Simple radiographs are used to exclude other causes of lower back or sciatic pain such as listhesis, fractures, and stenosis. Radiographic evidence of instability includes movement of 3 mm in the L1-4 vertebrae or 5 mm in the L5-S1 intervertebral space, or angulation of >10° in adjacent vertebrae [9.] In our study, all participating patients have been evaluated for instability, and those without instability have been included in our study.

Gadolinium-enhanced MRI is the preferred imaging method for evaluating recurrent lumbar disc herniation (LDH). This allows for the differentiation of recurrent disc herniation from other disease processes such as epidural fibrosis, arachnoiditis, abscess, and hematoma. Although theoretically the variables of recurrence and scar tissue can be identified in MRI, it's not always radiologically possible to distinguish

between recurrence and scar tissue under postoperative conditions (Figure 3). However, diagnosing recurrence becomes much easier when evaluated along with clinical signs. Indeed, if a patient whose postoperative pain has resolved subsequently experiences a return of pain, and if there is radiological compression consistent with the pain, decompression surgery is recommended. Therefore, MRI findings should be compared with the patient's complaints and physical examination. Radiological evaluation alone is not sufficient for a diagnosis of "recurrence," just as clinical evaluation alone would not be sufficient. Indeed, it has been shared in the literature that MRI findings can be abnormal in up to 20% of asymptomatic patients [16].

Numerous scholarly investigations underscore the critical need for differentiating between recurrent lumbar disc herniation (LDH) and epidural fibrosis. Furthermore, these investigations commonly assert that the presence of epidural scarring or fibrosis correlates with adverse clinical outcomes following subsequent surgical interventions [9-11, 16]. Characteristically, an epidural scar manifests an isointense appearance relative to the intervertebral space and demonstrates early heterogeneous uptake of contrast material. The anatomical interrelationship between the dura mater and the lesion predominantly involves traction of the dura mater towards the lesion. While the differentiation between an epidural scar and disc herniation holds clinical significance, the clinical implications of the presence of an epidural scar remain indeterminate. Research conducted by Rönnberg et al. indicates an absence of direct correlation between the existence of scar tissue and clinical outcomes [17].

In our study, two patients who were re-operated on due to the presence of symptomatic compression, despite the radiological interpretation of "scar tissue" in early-phase contrast-enhanced MRI, were considered to have "recurrent" cases based on significant improvement in their postoperative VAS scores (Figure 3). Although this specific point is not the primary focus of our study, the positive surgical outcomes in these two patients, who were initially diagnosed radiologically with 'Scar Tissue,' could contribute to ongoing debates in the literature regarding this issue [10, 11, 16, 17]. Consequently, our study defines recurrent LDH as follows: patients whose pain subsides following the initial surgery, exhibit no new symptoms during standing evaluations on the 20th day postoperatively, but later experience the re-emergence of radiculopathy symptoms. New MRI findings at the same level and on the same side as the initial surgery demonstrate radicular compression that aligns with the patient’s symptoms and neurological examination, are considered to have 'Recurrent LDH.'

5. Conclusions

Key findings of our study are as follows:

-Our study addresses the concept of early recurrence, delving into variables of this disconcerting topic for every surgeon.

-It emphasizes that the literature supports similar early recurrence risk profiles for both full endoscopic and microscopic techniques.

-Our study pioneers the utilization of a commonly used practical method for measuring the volume of the disc removed during surgery in the academic literature.

-It highlights the potential insignificance of the volume of the disc removed during surgery in the development of early recurrence (though, of course, this must be definitively stated through a comparison of surgeries performed at the same center).

-It provides recommendations for planning future studies (such as evaluating LDH patients who require surgery within the first three months, referred to as very early LDH surgery).

-Our study introduces an independent definition of "recurrent LDH" that is applicable to patients presenting with LDH recurrence, particularly within the first six months, regardless of the terms "scar tissue?", "recurrence?", or "residue?" in contrast-enhanced lumbar MRIs.

Limitations of the Study

We are aware of the limitations of our study. Specifically, its retrospective design and the limited number of patients necessitate caution in generalizing our findings. In future studies, it would be beneficial to assess the impact of these factors in larger patient populations and within a prospective design.

Acknowledgement

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Conflict of Interests

There are no conflicts of interest between the authors and the institutions.

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No.

Author Contributions

Study design: DKG, Sample collection: DKG, Data collection and/or Processing: DKG, BG, Writing Original Manuscript: DKG, BG, contributed to revising the work and providing approval of the final version of the manuscript.

Ethical Approval

This study, being a retrospective study, does not require ethical approval. However, it is currently under evaluation by the Selçuk University Faculty of Medicine Ethics Committee (04.09.2023).

Data sharing statement

Data supporting the findings of this study can be made available upon request from the corresponding author.

Consent to participate

Participation consent has been obtained from the patient and control groups involved in the study.

Informed Statement

Patients and control groups who agreed to participate in the study have signed the informed consent form.

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Prevalence of Allergic Diseases and Risk Factors in Preschool Children

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Abstract: Allergic diseases are very common in children. The aim of this study is to obtain information about the frequency and risk factors of allergic diseases in kindergarten children aged 3-6 years. This study was carried out between 13.02.2018 and 30.12.2018 in kindergartens, in accordance with the ISAAC Phase I protocol for children aged 3-6 years. The study was carried out by distributing 3000 questionnaires in 20 kindergartens. 2001 out of 2040 collected questionnaires were included in the study. Of the participants, 986 (49.3%) were female and 1015 (50.7%) were male. The frequency of asthma symptoms was 30.4% (n=608). The frequency of allergic rhinitis symptoms was found to be 37.1% (743 people). The risk of asthma symptoms was significantly higher in males, those whose mothers smoked during pregnancy, those born preterm, those with a smoker at home and those with mold in the home ($p<0.05$). The risk of allergic rhinitis symptoms was significantly higher in smokers and those with mold in the home ($p<0.05$ for both). The presence of smokers and mold were both risk factors for both allergic rhinitis and asthma symptoms. Awareness should be increased in families of high risk patients. ©2023 NTMS.

Keywords: Asthma; Allergic Rhinitis; Children.

1. Introduction

It is reported that there is a significant increase in the prevalence of childhood allergic diseases in the world. [1] Comparing the prevalence of allergic diseases with international systematic methods is necessary to understand the global epidemiology of these diseases, to generate new hypotheses and to evaluate the possible causes of existing hypotheses. Asthma is an important health problem worldwide and is the most common chronic disease of childhood in most countries [1-3]. Its prevalence in children reported to be as nearly 11.0% and varies between different age groups [4]. In the National Burden of Disease Study conducted in our country in 2000, it was reported that when the diseases were ranked in terms of burden, asthma was ranked fourteenth in urban areas with a rate of 1.3%, and it was ranked ninth in rural areas with a rate of 1.1% [5].

Allergic rhinitis (AR) or allergic rhinosinusitis is characterized by bouts of sneezing, runny nose, and nasal congestion, and is often accompanied by symptoms of itching in the eyes, nose, and palate [6]. In a study conducted in children aged 6-7 years in Türkiye, the frequency of AR was found to be between 2.9 and 43.5% [7].

In this study, we target to inform families about allergic diseases that occur and are frequently encountered in every four or five of our children, to help understand

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the importance of the disease [8,9]. With the questionnaire prepared in accordance with the ISAAC (International Study of Asthma and Allergy in Childhood) protocol[10], it was aimed to obtain information about allergic diseases among children and determine the frequency and risk factors of allergic diseases in preschool children between the ages of 3-6 years, and their distribution according to socio-demographic features.

2. Material and Methods

This cross-sectional type of study was planned to reach a population of 3,000 children aged 3-6 years by evaluating similar literature, and at least 70% of the population was screened. The study was carried out in kindergartens between 13.02.2018 and 30.12.2018. In the study, a total of 20 kindergartens were screened. 3.000 questionnaires were distributed under the control of teachers to be sent to their families. The teachers were given detailed information about the subject and the purpose of the survey. 2040 of the distributed questionnaires could be recollected five days later and 2001 questionnaires were included in the study since 39 questionnaires, which were determined to be filled inattentively, were not considered appropriate to participate in the study.

When creating the survey, demographic characteristics (age, gender), risk factors for allergic diseases (familial and environmental factors) and allergic disease symptoms, frequency and severity were included in the study questions in accordance with the ISAAC protocol. The frequency of allergic diseases were determined by ‘‘parents’s self report’’ via used questionnaire.

2.1. Statistical analysis

Statistical analysis was performed using the SPSS 22.0 for Windows (SPSS, Inc.; Chicago, USA) package program. Descriptive statistics are given as number (n), percent (%). Chi-square test was used to compare categorical variables. Logistic regression analysis was performed for the multivariate analysis. Statistical significance level was accepted as $p<0.05$.

2.2. Ethics

Ethics committee approval was obtained from the Ethics Committee of University of Kahramanmaraş Sütçü İmam Faculty of Medicine on 22.11.2017 with decision number 06.

Permission was obtained from the Directorate of National Education for the study to be carried out in schools.

3. Results

This study is carried out with the participation of 2001 children (3-6 years old) attending kindergarten to determine the frequency of allergic diseases and their risk factors. Of the participants, 986 (49.3%) were female and 1015 (50.7%) were male. Of the children, 6.2% (n=124) had mother who had smoked during pregnancy. The percentages of children having smokers and mold at home were 28.6% (n=573) and 7.8% (n=157), respectively. Other sociodemographic characteristics of the children participating in the study are given in Table 1.

Table 1: The sociodemographic characteristics of the children participating in the study.

	n	%
Gender		
Female	986	49.3
Male	1015	50.7
Did you smoke cigarettes during your pregnancy?		
Yes	124	6.2
No	1877	93.8
Did you have full-term pregnancy?		
Yes	1720	86.0
No	281	14.0
What type of birth did you have for your baby?		
Vaginal delivery	582	29.1
Cesarean birth	1419	70.9
Did your child go to kindergarten?		
No, she/he didn’t.	1729	86.4
Yes, she/he did.	272	13.6
Does anyone smoke at your home?		
Yes	573	28.6
No	1428	71.4
Do you have mold on the walls of the house you live in?		
Yes	157	7.8
No	1844	92.2

n=number, %=percentage.

The frequency of asthma symptoms was 30.4% (n=608). When the factors related to the development of asthma symptoms were evaluated, asthma symptoms were significantly more common in males, in children whose mothers smoked during pregnancy, and who was born pretermly and with cesarean sections (p<0.05). In addition, asthma symptoms were observed at a higher rate in children having smokers and mold at home and in those who attended kindergarten (p<0.05). The comparison of the sociodemographic characteristics of the children participating in the study with the asthma findings is given in Table 2.

Table 2: The comparison of the sociodemographic characteristics of the children participating in the study with the asthma findings.

	Has your child ever had a wheezing sound at his/ her chest while breathing?				
	No		Yes		p*
	n	%	n	%	
Gender					
Female	711	72.1	275	27.9	0.017
Male	682	67.2	333	32.8	
Did you smoke cigarettes during your pregnancy?					
No	1319	70.3	558	29.7	0.013
Yes	74	59.7	50	40.3	
Did you have full-term pregnancy?					
No	160	56.9	121	4.1	**<0.001**
Yes	1233	71.7	487	28.3	
What type of childbirth did you have for your baby?					
Cesarean birth	958	67.5	461	32.5	**0.001**
Vaginal delivery	435	74.7	147	25.3	
Did your child go to kindergarten?					
No, s/he didn't.	1221	70.6	508	29.4	**0.014**
Yes, s/he did.	172	63.2	100	36.8	
Does anyone smoke at your home?					
No	1032	396	396	27.7	**<0.001**
Yes	72.3	27.7	212	37.0	
Is there any mold on the walls of the bathroom or any room of the house you live in?					
No	1303	70.7	541	29.3	**<0.001**
Yes	90	57.3	67	42.7	

n=number, %=percentage, *Pearson's chi-square test.

The frequency of allergic rhinitis symptoms was found to be 37.1% (n=743). When the factors related to the development of allergic rhinitis symptoms were evaluated, allergic rhinitis symptoms were significantly more common in children who was born pretermly and with cesarean sections (p<0.05). In addition, allergic rhinitis symptoms were observed at a higher rate in children having smokers and mold at home and in those who attended kindergarten (p<0.05). The comparison of the sociodemographic characteristics of the children participating in the study with the findings of allergic rhinitis is given in Table 3. With the logistic regression test, the predictors of the presence of asthma symptoms were evaluated. The presence of smokers and mold at home were risk factors for asthma symptoms (p<0.001 for both). Other risk factors for asthma were male gender, having smoking mother during pregnancy and to be born pretermly (p=0.019, p=0.038, p<0.001). According to the logistic regression analysis, age, type of delivery, going to kindergarten had no signficant effect on asthma symptoms (Table 4).

Table 3: The comparison of the sociodemographic characteristics of the children participating in the study with the findings of allergic rhinitis.

	Has your child ever had problems of sneezing, runny or stuffy nose when they didn't have a cold or flu?				
	No		Yes		p*
	n	%	n	%	
Gender					
Female	640	64.9	346	35.1	0.063
Male	618	60.9	397	39.1	
Did you smoke cigarettes during your pregnancy?					
No	1188	63.3	689	36.7	0.127
Yes	70	56.5	54	43.5	
Did you have a full-term pregnancy?					
No	161	57.3	120	42.7	**0.037**
Yes	1097	63.8	623	36.2	
What type of childbirth did you have for your baby?					
Cesarean birth	869	61.2	550	38.8	**0.019**
Vaginal delivery	389	66.8	193	33.2	
Did your child go to kindergarten?					
No, s/he didn't.	1102	63.7	627	36.3	**0.043**
Yes, s/he did.	156	57.4	116	42.6	
Does anyone smoke at your home?					
No	926	64.8	502	35.2	**0.004**
Yes	332	57.9	241	42.1	
Is there any mold on the walls of the bathroom or any room of the house you live in?					
No	1172	63.6	672	36.4	**0.029**
Yes	86	54.8	71	45.2	

n=number, %=percentage, *Pearson's chi-square test.

Table 4: The evaluation of the predictors of the presence of asthma symptoms by the logistic regression analysis of the independent variables.

	B	Wald	p	OR	95% CI	
					Lower Limit	Upper Limit
Age	-0.010	1.565	0.211	0.990	0.975	1.005
Gender						
Male (ref.=female)	0.236	5.479	**0.019**	1.266	1.039	1.542
Did you smoke cigarettes during your pregnancy?	0.414	4.295	**0.038**	1.512	1.023	2.237
Yes (ref.=no)						
Did you have a full-term pregnancy?						
No (ref.=yes)	0.534	15.143	**<0.001**	1.705	1.303	2.231
Type of delivery						
Vaginal delivery (ref.= cesarean birth)	-0.160	1.903	0.168	0.852	0.678	1.070
Did your child go to kindergarten?						
Yes (ref.=no)	-0.211	2.167	0.141	0.810	0.612	1.072
Does anyone smoke at your home?						
Yes (ref.=no)	0.411	13.755	**<0.001**	1.508	1.214	1.873
Do you have mold on the walls of the house?	0.700	14.852	**<0.001**	2.014	1.411	2.875
Yes (ref.=no)						

OR=odds ratio, CI= confidence interval.

With the logistic regression test, the predictors of the presence of allergic rhinitis symptoms were evaluated. The presence of smokers and mold at home were risk factors for allergic rhinitis (p=0.002 and p=0.001, respectively). According to the logistic regression analysis, gender, to have smoking mother during pregnancy, to be born pretermly, type of delivery and going to kindergarten had no significant effect on allergic rhinitis symptoms (Table 5).

Table 5: The evaluation of the predictors of the presence of allergic rhinitis symptoms by the logistic regression analysis of the independent variables.

	B	Wald	p	OR	%95 CI	
					Lower Limit	Upper Limit
Gender Male (ref.=female)	0.183	3.664	0.056	1.200	0.996	1.447
Did you smoke cigarettes during your pregnancy? Yes (ref.=no)	0.312	2.473	0.116	1.366	0.926	2.016
Did you have a full-term pregnancy? Yes (ref.=no)	-0.156	1.333	0.248	0.855	0.656	1.115
Type of delivery Vaginal delivery (ref.=cesarean birth)	-0.045	0.174	0.676	0.956	0.772	1.183
Did your child go to kindergarten? Yes (ref.=no)	-0.111	0.644	0.422	0.895	0.683	1.173
Does anyone smoke at your home? Yes (ref.=no)	0.326	9.355	**0.002**	1.385	1.124	1.706
Do you have mold on the walls of the house? Yes (ref.=no)	0.587	10.302	**0.001**	1.799	1.257	2.576

OR=odds ratio, CI= confidence interval.

4. Discussion

In this study, the rate of wheezing in children during their childhood was found to be 30.4% (n=608). In a study conducted by Topal et al., on school children aged 6-7 years, the rate of wheezing in their childhood was found to be 20.3% [11]. Similar to the literature, we thought that approximately one third of the children in our study may have symptoms that may be caused by asthma at least once in their lifetime. In our study, the frequency of asthma symptoms was found to be higher in boys than in girls. Similarly, in the logistic regression analysis, asthma symptoms were found to be more frequent in boys than in girls in a statistically significant way. In a study conducted by Strannegard et al. the incidence of asthma was found to be higher in boys than in girls [12].

In the multicentric ISAAC Phase III study, conducted with children aged 6-7 years between 2002 and 2003, it was reported that the frequency of AR varied between 2.2-27.8% [13]. In the study of Akcay et al. the frequency of AR was reported as 33.5% and the frequency of physician-diagnosed AR as 6.1% [14]. In a different study, the prevalence of current AR in children aged 6–7 years was reported as 15.0% (95% CI:13.8–16.3%) [15]. In our study, the frequency of AR was 37.1% and the frequency of physician-diagnosed AR was found to be 14%. When we look at the literature, it has been observed that the frequency of AR varies among regions. We thought that the reasons for these differences were environmental factors, climatic changes, allergic predisposition of the patients, genetic predisposition, and the inability to differentiate allergic rhinitis from rhinoconjunctivitis.

In a study by Harju M et al. [16], it was concluded that smoking during pregnancy increases the risk of asthma in children, and quitting smoking significantly reduces this risk. In our study, we found a significant relationship between smoking during pregnancy and the presence of asthma symptoms at any time. Similarly, in the logistic regression analysis between smoking during pregnancy and allergic symptoms in our study; children of mothers who smoked during pregnancy had asthma symptoms more frequently than those who did not smoke. The results were statistically significant. In the study conducted by Turan M et al. a significant relationship was found between smoking during pregnancy and AR symptoms [17]. However, in our study, no significant relationship was found between smoking during pregnancy and AR symptoms. In our study, we concluded that children who were born by cesarean section developed asthma symptoms at a higher rate than those who were born by vaginal delivery. Similar to our study, in a cohort study conducted by Rusconi et al. [18] evaluating 67,613 deliveries from nine countries, it was concluded that the risk of asthma is higher in those born by cesarean

section. In a cohort study by Bager et al. [19] in Denmark, including 9,722 cases, it was concluded that cesarean delivery did not pose a risk for AR. On the other hand, in our study, the frequency of AR symptoms was found to be higher in children born by cesarean section. We thought that the reason for this difference was regional climate change and environmental factors.

The frequency of asthma symptoms was found to be higher in children born prematurely than those born after full-term pregnancy (43.1% vs 28.3%), in our study. Similar to the results of our study, in a study conducted by Matheson MC et al. [20], it was found that the prevalence of asthma in children born prematurely was higher in later ages compared to those born after full-term pregnancy. In the logistic regression analysis of our study, asthma symptoms were found to be more frequent in premature babies than in full term ones in a statistically significant way. In the study of Sucu et al., no significant relationship was found between premature birth and the appearance of AR symptoms. In our study, the frequency of AR symptoms was found to be higher in children born as premature compared to those born as full term at a statistically significant level.

In our study, the frequency of asthma symptoms was higher in children who went to kindergarten. In a study by Yeh KW et al. [21] that included 3863 children aged 3-6 years between 2007 and 2008, it was reported that there was an increase in the frequency of asthma symptoms in children who went to kindergarten, similar to our study. In our study, the frequency of AR symptoms was found to be higher in children who went to kindergarten. In a study conducted by Pekkanen et al. [22], it was concluded that the probability of AR is higher in children who attend kindergarten, similar to our study.

In a study conducted with parents of asthmatic children 28.2% of the parents were smokers [23]. In our study, we found a significant relationship between secondhand smoke exposure and asthma symptoms in childhood. As a result of a meta-analysis of 327 studies carried out by Saulyte J et al., it was concluded that exposure to cigarette smoking increases the risk of allergic diseases in children [24]. Similarly, in our study, we found a significant relationship between the occurrence of AR symptoms and smoking at home. In logistic regression analysis, a positive correlation was found between smoking at home and the occurrence of AR symptoms.

In our study, we found that the presence of mold in the house and the occurrence of asthma symptoms are associated with each other. Similarly, a positive correlation was found between the presence of mold in the house and the occurrence of asthma symptoms in the logistic regression analysis. In a study by Tarkan et al., it was reported that mold is among the important aeroallergens [25]. Similar to our study, in a study conducted by Civelek et al. in 2009, it was concluded that the presence of mold in the house increased asthma symptoms [26]. In a different study, it was reported that the presence of molds on bathroom walls leads 5% higher prevalence of allergic rhinitis. [27] We found that AR symptoms were seen at a higher rate in children exposed to mold in their houses. In the logistic regression analysis, a positive correlation was found between the presence of mold in the house and the occurrence of AR symptoms.

5. Conclusions

As a result, in our study, it is observed that the frequency of asthma symptoms is 30% and it is more common in male children. The frequency of allergic rhinitis is 37% and there is no significant difference between male and female children. It is observed that asthma and allergic rhinitis symptoms are more common in children who lived with mold in their home. The presence of smokers and mold at homewere both risk factors for both allergic rhinitis and asthma symptoms. Awareness should be increased in families of high risk patients. Precautions should be taken for the risk factors.

Limitations of the Study

The children in the study were participating from single city, thus results have limitation in reflecting the population of the whole country.

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Conflict of Interests

The authors declared no conflict of interest.

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Author Contributions

NS, UA and MYÖ designed the research. NS participated indata collection and data analysis. NS, UA and MYÖ wrote the manuscript, read and approved the final manuscript.

Ethical Approval

Ethics committee approval was obtained from the Ethics Committee of University of Kahramanmaraş Sütçü İmam Faculty of Medicine on 22.11.2017 with decision number 06.

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Not applicable.

Informed Statement

Informed consent was obtained from parents.

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