ISSN 2146-6505 • EISSN 2147-1894

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JOURNAL OF ACADEMIC RESEARCH IN MEDICINE

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VOLUME:12 ISSUE:1 APRIL 2022

UNIVERSITY OF HEALTH SCIENCES TURKEY GAZİOSMANPAŞA TRAINING AND RESEARCH HOSPITAL

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• **Publication Type:** Periodical

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Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publishing Date:
March 2022
ISSN: 2146-6505
E-ISSN: 2147-1894

International scientific journal published quarterly.

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DOI: 10.4274/jarem.galenos.2021.46320
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miRNA-129-3P Expression in Synovial Fluid of Patients with Osteoarthritis

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Cite this article as: Bozdoğan Polat SH, Polat A, Uzun H, Şahin G, Darıyerli N. miRNA-129-3P Expression in Synovial Fluid of Patients with Osteoarthritis. J Acad Res Med 2022;12(1):1-4

ABSTRACT

Objective: The aim of this study was to investigate the miRNA-129-3p expressions in the synovial fluid of patients with a primary knee osteoarthritis (OA), and thereby contribution to the elucidating underlying molecular mechanisms in OA pathophysiology.

Methods: Patient group included 31 individuals with an advanced knee OA. A total of 13 patients with anterior cruciate ligament rupture who had no cartilage damage, were chosen as a control group. Synovial fluid samples were collected during the total knee arthroplasty and an arthroscopic reconstruction. After the centrifugation, samples were stored in a -80 °C cooler. The miRNA-129-3p expressions were examined by reverse transcriptase-polymerase chain reaction using the RNU44 molecule as a reference. The 2-ΔΔCt method was used to calculate the expression of molecules. Statistical comparisons were undertaken by the Student's t-test. Pearson's chi-square test was used to determine the differences in the ratios or relationships between the categorical variables. Statistical significance was set at $p<0.05$ for all the cases.

Results: In this study, the miRNA-129-3p, which we thought to be associated with the ciliogenesis, IL-17, and osteoprotegerin, was found 1.54 times higher in the synovial fluid of the patients compared to a control group ($p<0.01$).

Conclusion: It is thought that the miRNA-129-3p may play a role in the OA pathophysiology. Extensive studies are required to use the miRNA-129-3p as a biomarker, or a treatment target for OA.

Keywords: Osteoarthritis, miRNA-129-3p, ciliogenesis, synovial fluid

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Received Date: 27.02.2021 **Accepted Date:** 05.12.2021

J Acad Res Med 2022;12(1):1-4

INTRODUCTION

It is widely unknown how the path of mechanical transformation in osteoarthritis (OA) changes, and how chondrocytes perceive and respond to the compression. A recent study suggested that the primary cilia of chondrocytes played a role in detecting and transmitting the mechanical stimulation such as (1): McGlashan et al. (2) reported that in normal cartilage cells, the number and length of the cilia were the lowest in the superficial zone and increased as they moved away from the articular surface. This was the first study showing that the primary cilia are present in chondrocytes during the OA progression, and that the total percentage of cilia cells in degenerative cartilage increased with the OA severity (2). Cao et al. (3) reported that the ciliary genesis of miRNA-129-3p was regulated by the actin dynamics and CP_{110}, a ciliary gene blocker. The removal of the CP_{110} promoted the growth of a ciliary axoneme. The authors suggested that the miRNA-129-3p increased the formation of cilia by reducing the CP_{110} (3).

Tsai et al. (4) showed that the miRNA-129-3p was the most repressed miRNA with its IL-17 binding potential after the stimulation of the osteoblasts by osteopontin in the arthritis model. In the same study, the miRNA-129-3p in osteoblasts was reported to bind directly to the 3′-UTR region of the *human IL-17* gene, suppressing IL-17 translation and eliminating the monocyte migration (4). In another study by Liu et al. (5), found that synovial IL-17 levels were significantly higher in the OA patients compared to the control group, and showed a negative correlation with the OA severity. IL-17 has also been reported as a pain sensitizer in the rodent models of arthritis (6).

The studies demonstrate that the miRNA-129-3p may play a role in the cartilage degeneration and inflammatory cascade of the OA and provides insight into a potential miRNA-based treatment strategies for delaying the hyperalgesia and the regulation of ciliary functions by IL-17 mediated monocyte migration. In our study, we aimed to investigate the differences in the expression of a synovial fluid in the patients with an advanced OA, considering the role of miRNA-129-3p in IL-17-osteopontin relationship and ciliogenesis. To the best of our knowledge, the literature does not contain any microarray studies on OA conducted with these expectations.

METHODS

This research experiment was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient prior to the study. The necessary approval was obtained from the Faculty Ethics Committee of Istanbul University-Cerrahpaşa (decision no: 83045809-604.01.02, date: 05.09.2017).

The study has two groups: patient, and control group. All the participants presented to our orthopedics clinic in 2017 and 2018. Patient group included 31 individuals with an advanced primary knee OA. They were classified into stage 3-4 OA according to the Kellgren-Lawrence classification (5). Thirteen patients with an anterior cruciate ligament (ACL) rupture were chosen as a control group. During the arthroscopic reconstruction, ACL rupture cases evaluated as stage 0, both according to Kellgren-Lawrence and Outerbridge classifications were included in the control group. The gender distribution of the participants is 17 men [8 patients (47.1%) and 9 controls (52.9%) p=0.018] and 27 women [23 patients (85.2%) and 4 controls (14.8%) p=0.033]. Synovial fluid used as a material. Patients with the malignancies, systemic infection, poor general condition, cognitive dysfunction, or psychosis, under 18 years of age, pregnant women, puerperal and breastfeeding women were excluded.

The synovial fluid of the patient and control groups were collected on a voluntary basis within the framework of the ethical rules. Volunteers in both the groups were clearly informed about the purpose and content of the study before the participation. A full physical examination was performed in all the patients. The direct radiographs and the magnetic resonance imaging of the groups were examined. Routine blood tests were evaluated before the operation.

A total of 1.5-3 mL of synovial fluid was taken from the participants. The materials were centrifuged at 3,000 g for 5 mins; then, the supernatant was transferred to the different Eppendorf tubes and stored in a -80 °C cooler until the day of the experiment. Total RNA isolation was performed with an EXTRACTME miRNA kit. The isolated RNAs were evaluated by a nano spectrophotometer prior to the complementary DNA (cDNA) synthesis. A TRANSCRIPTME RNA kit was used for cDNA synthesis from the template RNA. In the last step, miRNA was evaluated by the real-time polymerase chain reaction (PCR) method.

Statistical Analysis

In the mean ± standard deviation (SD) comparisons, the Student's t-test was used by providing the necessary conditions such as: normal distribution and covariance. Pearson's chi-square test was conducted to determine the differences in the ratios or relationships between the categorical variables. Statistical significance was set at $p<0.05$ for all the cases.

RESULTS

In this study, miRNA-129-3p expression in the synovial fluid of the patients was found to be 1.54 times higher than the control group ($p<0.01$) (Table 1) (Figure 1). Age was significantly different in the patient group compared to the control group (mean ± SD patient age: 62.77±5.42, control age: 33.15±8.91, $p<0.001$) (Table 1). Body mass index (BMI) was significantly higher in the patient group compared to the control group (mean ± SD patient BMI: 32.34±6.58, control BMI: 25.86±2.45, $p<0.001$).

DISCUSSION

In this study, the miRNA-129-3p, which we thought to be associated with the ciliogenesis, IL-17, and osteoprotegerin (OPN), was found

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Table 1. Mean ± standard deviation, median, and p-values of the data obtained from the patient and control groups

	Control Median ± SD	Patient Median ± SD	-
	Control Median (min-max)	**Patient Median (min-max)**	**p**
Age	33.15±8.91	62.77±5.42	0.001
	35 (18-47)	63 (53-72)	-
Length	168.62±5.72	163.97±7.07	0.06
	168 (160-178)	165 (150-180)	-
Weight	73.62±8.26	86.29±14.25	0.002
	78 (55-85)	85 (65-135)	-
BMI	25.86±2.45	32.34±6.58	0.001
	26.1 (21.5-29.4)	31.2 (23.9-52.7)	-
ΔCT	-3.44±0.64	-4.06±0.77	0.01
	-3.35 (-4.98 to -2.57)	-4.24 (-5.74 to -2.07)	-

BMI: body mass index, min: minimum, max: maximum, SD: standard deviation

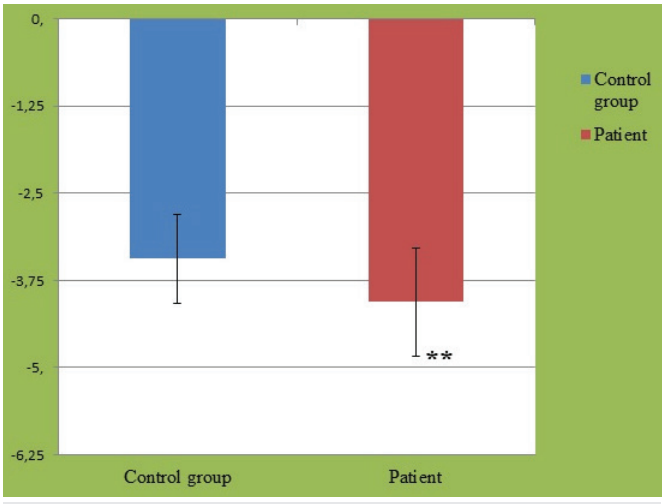

Figure 1. Comparison of the ΔCT values of the advanced osteoarthritis and control groups**

1.54 times higher in the synovial fluid of the patients compared to a control group (p<0.01).

In a study by McGlashan et al. (2), primary cilia were found in chondrocytes during the OA progression, and the total percentage of cilia cells in a degenerative cartilage increased with the OA severity (1). Cao et al. (3) suggested that the increased expression of miRNA-129-3p increased cilia cells by regulating the CP_{110} and actin dynamics. The number and length of a primary cilia in the degenerative joint chondrocytes increased in OA (2). The miRNA-129-3p is defined micro-RNA that increases in the ciliogenesis over CP_{110} inhibition (3). Therefore, the high expression of miRNA-129-3p in the synovial fluid in patients with an advanced OA may also be related to the ciliogenesis.

OPN and IL-17 are known to be involved in the pathogenesis of OA (5,7). Tsai et al. (4) showed that the human *IL-17* gene was one of the target genes of the miRNA-129-3p. They reported that the miRNA-129-3p expression was decreased through the Syk-PI3K-Akt pathway, and increased IL-17 because of the osteoblast stimulation by an osteopontin (4). Thus, it could be stated that the OPN and IL-17 are associated with the miRNA-129-3p.

In a study performed by Liu et al. (5) with 226 OA patients and 106 control subjects, the IL-17 levels were found to be negatively correlated with the OA severity. In another study, Snelling et al. (8) found that in 152 patients with an advanced OA, the IL-17 levels were elevated only in the 14 patients, while IL-17 could not be detected in 138 patients. The reduced levels of IL-17 in the OA patients in these studies may be associated with an increase in the miRNA-129-3p in an advanced OA, and its consequent binding to the *IL-17* gene and reduced IL-17 translation.

Dong et al. (7) found that the osteopontin levels decreased in patients with an advanced OA. Matsui et al. (9) showed that the osteopontin deficiency exacerbated both aging-related and instability-induced OA. Decreased levels of osteopontin in the OA may be associated with the increased miRNA-129-3p levels. These studies indirectly support our thesis.

It is known that increase in the mechanical load due to obesity and aging take place in the etiology of OA (10). In our study, BMI was found to be significantly higher in the advanced OA group compared to the control group (32.34±6.58 and 25.86±2.45, respectively; p<0.001). It is known that the risk of OA increases by 60% in a people with the BMI of ≥30 (10). The increase in miRNA-129-3p expression is prominent in OA patients with a BMI of >30, suggesting that this expression is associated with the obesity. In our study, age was also significantly different in the advanced OA group compared to the control group (62.77±5.42 and 33.15±8.91, respectively; p<0.001). Age may also play an important role in the increase of the miRNA-129-3p.

Study Limitations

Limitations of our research were the limited number of participants in the patient and control groups, as well as the lack of homogeneity among the groups, the ability to test miRNA-129-3p expression only in the synovial fluid (could also be tested in a peripheral blood), and the lack of examination of the other mediators associated with OA pathogenesis, such as OPN, IL-17.

CONCLUSION

OA is a degenerative joint disease with a chronic inflammation and increasing global prevalence. There are symptomatic and surgical treatment options for this condition. Symptomatic treatment does not affect the progression of the disease, but the surgical treatments also have certain disadvantages. The molecular mechanism of the disease has not yet been fully elucidated. Recent studies showed that the miRNAs played an important role in the pathogenesis of the disease. Although the miRNA expression differences in the OA patients have been shown in studies, there is still a limited information about the varying levels of circulating miRNA. The miRNAs have been found to reduce inflammation,

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and OA progression or have anabolic function in the cartilage. It is considered that the injectable form of these miRNAs may be developed for the local treatment of OA in the joints. Thus, it is anticipated that the miRNA-based therapy may provide another approach to the treatment process without the potentially harmful side effects. In our study, the increased expression of miRNA-129-3p in an advanced OA patients compared to the control group indicates that the miRNA-129-3p may be involved in the pathogenesis of the OA. However, further prospective studies are needed for miRNA-129-3p to be used as a biomarker in the OA or as a therapeutic target.

Ethics Committee Approval: The necessary approval was obtained from the Faculty Ethics Committee of Istanbul University-Cerrahpaşa (decision no: 83045809-604.01.02, date: 05.09.2017).

Informed Consent: Written informed consent was obtained from each patient prior to the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - S.H.B.P., A.P., H.U., N.D., G.Ş.; Concept - S.H.B.P., A.P., H.U., N.D., G.Ş.; Design - S.H.B.P., H.U., N.D., G.Ş.; Data Collection and/or Processing - S.H.B.P., A.P.; Analysis and/or Interpretation - S.H.B.P., A.P., H.U.; Literature Search - S.H.B.P.; Writing - S.H.B.P., A.P.

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

Financial Disclosure: This study was funded by the Scientific Research Projects Coordination Unit of İstanbul University-Cerrahpaşa (project number: 27416).

Etik Komite Onayı: İstanbul Üniversitesi-Cerrahpaşa Fakülte Etik Kurulu'ndan gerekli izin alındı (karar no: 83045809-604.01.02, tarih: 05.09.2017).

Hasta Onamı: Çalışmadan önce her hastadan yazılı bilgilendirilmiş onam alındı.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazar Katkıları: Cerrahi ve Medikal Uygulama - S.H.B.P., A.P., H.U., N.D., G.Ş.; Konsept - S.H.B.P., A.P., H.U., N.D., G.Ş.; Dizayn - S.H.B.P., H.U., N.D., G.Ş.; Veri Toplama veya İşleme - S.H.B.P., A.P.; Analiz veya Yorumlama - S.H.B.P., A.P., H.U.; Literatür Arama - S.H.B.P.; Yazan - S.H.B.P., A.P.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Bu çalışma, İstanbul Üniversitesi-Cerrahpaşa Bilimsel Araştırma Projeleri Koordinasyon Birimi tarafından finanse edilmiştir (proje numarası: 27416).

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DOI: 10.4274/jarem.galenos.2021.28199
J Acad Res Med 2022;12(1):5-9

The Effects of Allergic Rhinitis on Sleep Quality

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Cite this article as: Çakan D, Öztürk E. The Effects of Allergic Rhinitis on Sleep Quality. J Acad Res Med 2022;12(1):5-9

ABSTRACT

Objective: This study aimed to examine the effects of allergic rhinitis (AR) on sleep quality (SQ).

Methods: This prospective study evaluated the AR symptoms and skin prick tests (SPT) in all participants. The AR group was composed of 65 male patients with AR symptoms and positive SPT, whereas the control group was composed of 65 healthy male individuals. SQ was evaluated using the Sleep Quality Scale (SQS). The AR group was asked whether AR affects their sleep, and those who answered yes were asked for the symptoms that affect their SQ. The SQS scores and the effect of symptoms on SQ were statistically compared.

Results: The mean SQS score of the groups was 68.68±13.15 in the AR group and 47.72±9.3 in the control group. The SQS score was significantly higher in the AR group compared to that of the control group ($p=0.002$, $p<0.05$). Of the patients, 30 (46.1%) had their sleep affected. The distribution of symptoms, which affect the SQ of these patients, was determined. Congestion is the most common symptom that affects the SQ, which was statistically significantly higher compared to other symptoms ($p=0.0001$, $p<0.05$).

Conclusion: AR is a risk factor for poor SQ. Patients with sleep disturbances should be questioned for AR and they should be provided with necessary treatment.

Keywords: Allergic rhinitis, quality of life, sleep, sleep-wake disorders, questionnaires

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Received Date: 02.08.2021 **Accepted Date:** 13.12.2021

J Acad Res Med 2022;12(1):5-9

INTRODUCTION

Allergic rhinitis (AR) is the most common allergic disease that affects up to 40% of the worldwide population (1). The classic AR symptoms include nasal congestion, rhinorrhea, sneezing, and itching (2). AR affects the patients' quality of life (QOL) in many areas, such as academic, athletic, and work performance (3-5).

Sleep quality (SQ) is a term without a precise definition but is defined as not having problems in initiating and maintaining sleep, having a satisfactory level of sleep experience and amount, and not having insomnia during the day (6). SQ evaluation differs, as well as its definition. Objective tests, such as polysomnography or subjective questionnaires, can be used to evaluate the SQ that affects the QOL (7,8). The SQ was commonly measured by the Pittsburgh Sleep Quality Index (PSQI) in the previous studies (9,10). The Sleep Quality Scale (SQS) is a self-reported questionnaire that consists of 28 questions and 6 factors, including difficulty in falling asleep, maintaining sleep, and getting up, restoration after sleep, sleep satisfaction, and daytime dysfunction, which is strongly correlated with PSQI results (10,11).

SQ is affected by many physiological and pathological conditions, such as nutrition, exercise, obesity, and asthma (8,12-14). Prior studies have shown that AR is related to SQ, and sleep disorders, such as obstructive sleep apnea, sleep-disordered breathing (SDB), enuresis nocturna, shorter sleep, and daytime dysfunction (15). This study aimed to examine the relationship between AR and SQ and discuss its related literature.

METHODS

The present study was conducted on patients and volunteers at İstanbul University-Cerrahpaşa Medicine Faculty Hospital and İnegöl State Hospital between November 2020 and September 2021 with the approval of the Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (decision no: 604.01.02-177955, date: 08.09.2021). The study design was a prospective cohort.

Study Population, Inclusion, and Exclusion Criteria

All study participants were followed at the Otorhinolaryngology Clinic of the Cerrahpaşa Medicine Faculty Hospital and Inegol State Hospital. SQ and AR are known to be affected by gender, thus only males were included in the study (10,16). Male patients with AR symptoms and positive skin prick test (SPT) for nonseasonal allergens (negative in SPT for grass, cereal, weed, and tree pollen extracts) were included as a patient group.

The exclusion criteria were as follows: ages below 18 or over 59 years, insufficient mental capacity, previous or active psychiatric disorders (e.g., depression), chronic disease (especially asthma), regular use of any medication (including anti-allergic drugs in the past 6 months), body mass index (BMI) of ≥30 kg/m^2, alcohol dependence, smoking, and refusal to enter the study or to complete the questionnaire.

Healthy males, who applied to the hospital for routine recruitment procedures, were included as the control group, with similar exclusion criteria as the patient group. Informed consent forms were obtained from patients and healthy individuals.

Sample Size and Sampling Technique

The minimum sample size was estimated based on the study of Kim et al. (17). The minimum sample size with an 80% confidence interval and 5% tolerable error assumptions was 65 for each group. Thus, 65 patients were included in the study group and 65 healthy individuals in the control group.

Procedures and Data Collection

All patients with AR were evaluated for allergic symptoms, with endoscopic nasal examinations, as well as BMI and SPTs. The SPT was performed according to the European Academy of Allergology and Clinical Immunology guidelines to support the diagnosis of allergy and determine the allergen or allergens in disease etiology (18). The SPT has been performed with mite (Dermatophagoides pteronyssinus and Dermatophagoides farinae), fungi (Cladosporium, Aspergillus, Penicillium, and Alternaria), weeds (Plantago Lanceolata, Artemisia Vulgaris, Taraxacum Vulgare, and Urtica Dioica), animal fluff (dog and cat), grasses (Dactylis Glomerata, Phleum Pratense, Hulcus Lanatus, Poa Pratensis, Lolium Perenne, and Festuca Pratensis), tree pollens (Fraxinus Excelsior, Quercus Robur, Ulmus Scabra, Alnus Glutinosa, and Olea Europaea), grains (Secale Cerela, Hordeum Vulgare, Triticum Sativum, and Avena Sativa) and food allergens (banana, cocoa, egg, fish, and nuts), and latex and cockroach extracts (Prick test kit, Stallergenes Greer, France). Histamine (10 mg/mL) was used as a positive control. The reactions were reported after 20 min by the investigator who performed the test. SPT was evaluated according to the induration diameter, wherein diameters of 3 mm and larger were accepted as positive.

SQ was assessed using the SQS, which consists of 28 questions. The scoring was done using a four-point, Likert-type scale, and respondents indicate how frequently they exhibit certain sleep behaviors (0= few, 1= sometimes, 2= often, and 3= almost always). Scores on items in factors 2 and 5 (restoration after sleep and sleep satisfaction) are reversed before being tallied. Total scores can range from 0 to 84. The higher scores show more acute sleep impairments (11).

The patient group was asked whether AR affects their SQ, and those who answered yes were asked for the symptoms (nasal congestion, rhinorrhea, sneezing, and itching) that affect their sleep. The frequency was calculated according to the responses and symptoms. The effect of symptoms on SQ was statistically compared.

Statistical Analysis

The minimum sample size was calculated using the G* Power software version 3.1 (19). The Statistical Package for the Social Sciences software version 21.0 (SPSS Inc, USA) was used for

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statistical analysis. Normal distribution of data was analyzed with the Kolmogorov-Smirnov test and Levene's tests to assess homogeneity. The independent samples t-tests (for continuous variables) and the Pearson chi-square test (for categorical variables) were used to compare the groups. The statistically significant level was accepted as a p-value of <0.05.

RESULTS

All individuals in the AR (group 1) and control (group 2) groups have completed the study. The mean ages of groups were 32.35±8.86 years in group 1 and 32.29±9.32 years in group 2. The mean BMI was 23.42±1.67 in group 1 and 23.10±1.37 in group 2. No statistically significant difference was found between the groups according to age and BMI (p>0.05) (Table 1). The evaluation of AR symptoms revealed nasal congestion in 45 (69.2%) patients, rhinorrhea in 35 (53.8%), itching in 27 (41.5%), and sneezing in 20 (30.8%).

The mean SQS score was 68.68±13.15 in group 1 and 47.72±9.3 in group 2. The SQS score was statistically significantly higher in group 1 compared to group 2 (p=0.002, p<0.05) (Table 2).

The frequency of "YES" answer for the question "Does your rhinitis affect your SQ?," is 30 (46.1%). The distribution of symptoms, which affect the SQ of these patients, was determined. Congestion is the most common symptom that affects the SQ, which was, statistically significantly higher compared to other symptoms (p=0.0001, p<0.05) (Table 3).

Table 1. Investigation of age and body mass index in groups

Group	Age Mean ± SD (min-max)	BMI Mean ± SD (min-max)
Group 1	32.35±8.86 (18-48)	23.42±1.67 (68-98)
Group 2	32.29±9.32 (18-49)	23.10±1.37 (68-98)
p*	0.291	0.346

*Independent samples t-test, BMI: body mass index, SD: standard deviation, min: minimum, max: maximum

Table 2. Evaluation of groups according to the Sleep Quality Scale

	Group 1	Group 2	p-value
SQS Mean ± SD (min-max)	68.68±13.15 (40-84)	47.72±9.3 (31-72)	0.002*

*Independent sample t-test, p<0.05. SQS: Sleep Quality Scale, SD: standard deviation, min: minimum, max: maximum

DISCUSSION

Sleep, which is very important for human psychology, cognitive functions, and the immune system, is necessary for body renewal and energy restoration (20,21). SQ is sometimes used to express measurement values that are obtained from objective tests, such as total sleep time, sleep onset latency, total wake time, sleep efficiency, and sleep disruptive events, and it is sometimes used to express the onset of sleep, the ability to continue sleep, the duration of sleep, and sleep-related problems during the day, which are stated by the person (22). Poor SQ or sleep disorders, which are related to chronic diseases, such as diabetes mellitus and cardiac diseases, even an increased risk of mortality, directly affect daytime performance and QOL (23-25). SQ is affected by many factors of the person or the environment. AR is one of the factors that have been shown to affect sleep in previous studies (15). Our study evaluated the SQ of patients with AR using the SQS

Table 3. Symptoms and sleep quality

Symptom		Entity			p-value
		Yes	No	Total	
Congestion	Count	25	5	30	0.0001*
	% within symptom	83.3%	16.7%	100.0%	
	% within entity	43.9%	7.9%	25.0%	
Rhinorrhea	Count	20	10	30	
	% within symptom	66.7%	33.3%	100.0%	
	% within entity	35.1%	15.9%	25.0%	
Sneeze	Count	5	25	30	
	% within symptom	16.7%	83.3%	100.0%	
	% within entity	12.3%	36.5%	25.0%	
Itching	Count	7	23	30	
	% within symptom	23.3 %	76.7%	100.0%	
	% within entity	12.3%	36.5%	25.0%	
Total	Count	57	63	120	
	% within symptom	47.5%	52.5%	100.0%	
	% within entity	100.0%	100.0%	100.0%	

*Pearson chi-square: 38.329, df: 3, p<0.001, df: degree of freedom

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questionnaire and compared it with the SQ of healthy individuals and a statistically significantly poor SQ in the AR group.

Many studies have been conducted with many different methods to evaluate the SQ, which affects every aspect of QOL. Polysomnography, which is the gold standard for sleep assessment, and actigraphy can be given as examples of objective tests. However, the objective methods are expensive and complex, with longer test times. Therefore, self-report methods, such as sleep diary and sleep questionnaires, in which SQ is evaluated by the individual, were used in various studies (7,8). SQS is one of these questionnaires whose validity has been demonstrated by previous studies (10,11) Our study used the SQS questionnaire to examine the relationship between AR and SQ as first in the literature. SQ is affected by age, gender, BMI, and psychological health (10). Study groups with people of the same sex, age, and BMI were formed to avoid these effects and ensure standardization.

Previous studies revealed that AR-associated sleep problems frequently include sleep apnea, SDB, shorter sleep duration, snoring, and poor SQ, and these problems are more common in patients with perennial AR than seasonal AR, and the presence of these problems indicates treatment inadequacy. Additionally, sleep problems are associated with all AR symptoms and are more common in patients with more severe symptoms. However, these problems are most commonly associated with the presence of nasal congestion (15,26). Our study, consistent with the literature, revealed nasal congestion as the most common symptom and the symptom that most affects the SQ in patients with AR.

AR is known to affect SQ; however, the underlying mechanisms of sleep disorders are still undetermined. Additionally, this effect is thought to be caused by the inflammatory mediators that increase in AR, the direct effects of AR symptoms on sleep, and the autonomic nervous system changes seen in patients with AR (15). Previous studies have shown that inflammatory mediators, especially histamine, which increases in AR, directly affect the central nervous system and cause sleep disorders, such as daytime sleepiness (15,27). Moreover, the decrease in cytokines, such as interleukin (IL)-4, IL-6, and IL-10 in AR, which is known to have positive effects on the REM period, and is the most important stage of sleep, is associated with SQ deterioration (28). Nasal congestion, which is the most common symptom of AR, causes increased nasal resistance, and nasal obstruction (15). Therefore, it is the most common AR symptom associated with sleep disorders, especially snoring (29). Cough and sputum production, along with other common symptoms of AR, also contribute to poor SQ (30). The trigeminocardiac reflex is one of the most powerful autonomic reflexes and is thought to be directly related to nasal congestion and sleep apnea (31).

Study Limitations

The present study has some limitations. First, in this study, the frequency of symptoms and how often they affect the SQ was determined. However, the severity of AR and the duration of symptoms, perineal or seasonal, which are directly related to the SQ, were not examined. Secondly, a subjective method, the SQS questionnaire, was used in determining the SQ. Finally, we only included males in the study to avoid gender-related effects.

CONCLUSION

A relationship was found between AR, which is the most common allergic disease and increasing in prevalence in the community, and SQ, one of the most important factors that affect the QOL. Investigating the presence of AR in patients with sleep disorders and questioning the SQ of patients with AR is necessary. The repetition of the obtained data with larger numbers of subjects and comprehensive clinical studies are required to support the present findings.

Ethics Committee Approval: The present study was conducted on patients and volunteers at Istanbul University-Cerrahpaşa Medicine Faculty Hospital and İnegöl State Hospital between November 2020 and September 2021 with the approval of the Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (decision no: 604.01.02-177955, date: 08.09.2021).

Informed Consent: Informed consent forms were obtained from patients and healthy individuals.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - E.Ö.; Concept - D.Ç.; Design - D.Ç.; Data Collection and/or Processing - D.Ç., E.Ö.; Analysis and/or Interpretation - D.Ç.; Literature Search - D.Ç.; Writing - D.Ç.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma, Cerrahpaşa Tıp Fakültesi Klinik Araştırmalar Etik Kurulu onayı (karar no: 604.01.02-177955, tarih: 08.09.2021) ile İstanbul Üniversitesi-Cerrahpaşa Tıp Fakültesi Hastanesi'nde ve İnegöl Devlet Hastanesi'nde Kasım 2020-Eylül 2021 tarihleri arasında hasta ve gönüllüler üzerinde yapılmıştır.

Hasta Onamı: Hastalardan ve sağlıklı bireylerden bilgilendirilmiş onam formları alındı.

Hakem Değerlendirmesi: Editörler kurulu ve editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazar Katkıları: Cerrahi ve Medikal Uygulama - E.Ö.; Konsept - D.Ç.; Dizayn - D.Ç.; Veri Toplama veya İşleme - D.Ç., E.Ö.; Analiz veya Yorumlama - D.Ç.; Literatür Arama - D.Ç.; Yazan - D.Ç.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

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DOI: 10.4274/jarem.galenos.2021.63825
J Acad Res Med 2022;12(1):10-4

Evaluation of Clinical, Laboratory and Radiological Findings in the Differential Diagnosis of Premature Telarche and Central Puberty Precocious

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Cite this article as: Peltek Kendirci HN, Kaba İ. Evaluation of Clinical, Laboratory and Radiological Findings in the Differential Diagnosis of Premature Telarche and Central Puberty Precocious. J Acad Res Med 2022;12(1):10-4

ABSTRACT

Objective: Central puberty precocious (CPP) is defined as the development of secondary sex characters due to the activation of the hypothalamus-pituitary-gonadal axis before the age of eight in girls. Premature telarche (PT) is defined as isolated breast development in girls without other findings of puberty. We aimed to evaluate the clinical, laboratory and radiological findings used in the differential diagnosis of PT and CPP.

Methods: The study included girls who applied to our pediatric endocrinology outpatient clinic between December 2015 and December 2019 with the complaint of breast enlargement that started before the age of 8 years and were diagnosed with SPP or PT. Retrospectively, patients' calendar age, bone age, bone age/calendar age ratio, anthropometric variables, puberty stages, luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol levels, ovarian and uterine volumes were examined.

Results: The study included sixty-five girls 53.8% PT (n=35) and 46.2% CPP (n=30). Height standard deviation (SD) values (p=0.008), basal LH, FSH and estrodiol levels (p=0.029, p=0.008, p=0.011, respectively), right and left ovaries and uterine volumes (p=0.030, p=0.008, p=0.039 respectively) bone age (p=0.039), and bone age/calendar age ratios (p=0.024) were found different between two groups. The importance order of the parameters used in the differential diagnosis of CPP and PT was found as basal LH level, ovarian volume, height SD value, and estrodiol level.

Conclusion: In our study, ıt was determined that our patients with CPP were taller than their peers with PT, had higher LH, FSH and estrodiol levels, larger ovarian and uterine volumes, higher bone ages and higher bone age/calendar age, and the most important parameter in diagnosis was basal LH level.

Keywords: Precocious puberty, breast, puberty, girls, secondary sex characters, differential diagnosis

Presented in: XXIV. Presented as a poster at the National Pediatric Endocrinology and Diabetes Online Congress.

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Received Date: 24.03.2021 **Accepted Date:** 16.12.2021

J Acad Res Med 2022;12(1):10-4

INTRODUCTION

Puberty is a transitional period accompanied by the development of secondary sex characteristics and psychosocial maturation. Precocious puberty (PP) is a clinical condition characterized by the early development of secondary sex characters compared to the population average. Early puberty can be classified as central precocious puberty (CPP), peripheral PP, and variants of normal puberty (1,2). CPP is defined as the development of secondary sex characteristics due to the activation of the hypothalamus-pituitary-gonadal (HPG) axis before the age of eight in girls and nine in boys (3-5).

Premature thelarche (PT) is isolated breast development before the age of eight without other clinical signs of puberty. PT is considered a variant of normal puberty, is not considered pathological, and is usually self-limiting, does not cause acceleration in skeletal development and shortens the time to completion of puberty. PP, on the other hand, results in early and rapid skeletal development and premature closure of the epiphyses, leading to a shorter final height of children compared to their genetic potential. In addition, 13% of PT cases may progress to PP (4). Distinguishing these two conditions is important for early diagnosis and treatment of PP (6). In our study, it was aimed to evaluate the clinical, laboratory and radiological findings used in the differential diagnosis of PT and CPP.

METHODS

The study included girls who applied to the pediatric endocrinology outpatient clinic of our hospital between December 2015 and December 2019 with the complaint of breast enlargement that started before the age of 8 and were diagnosed with CPP or PT (age matched with the group diagnosed with CPP). Retrospectively, patients' calendar age (years), bone age (years), bone age/calendar age ratio, anthropometric variables [body weight, height, body mass index (BMI) and standard deviation scores (SDS)], pubertal stages, luteinizing hormone (LH) level, follicle stimulating hormone (FSH) level and estradiol (E_2) level, and ovarian and uterine volumes evaluated by pelvic ultrasonography (USG) were examined.

Anthropometric measurements were made with the child's shoes and top clothes removed and in the morning on an empty stomach. Body weight was recorded as "kg" and height as "cm" by measuring with a stadiometer. Body weight and height SDS values were calculated (7). BMI; SDS values were calculated by calculating BMI= body weight (kg)/height $(m)^2$ formula (8). All patients were examined by the same pediatric endocrinologist and their pubertal stage was determined, pubertal staging was performed according to the Marshall and Tanner method (9). Bone age was evaluated according to the Greulich-Pyle method (10).

Uterine length, endometrium thickness, and three-dimensional measurements of the ovary from the suprapubic USG were recorded retrospectively. Uterine and ovarian volumes were calculated according to the longitudinal ellipsoid model with the formula (cm) x transverse diameter (cm) x 0.5236.

Among the girls who applied with breast development that started before the age of 8; cases with pubertal response to the LH-releasing hormone (RH) stimulation test applied to patients with advanced somatic development and advanced bone age (bone age more than 2 SDS according to the chronological age) were considered SPP (peak LH ≥5 mIU/mL). Cases that did not meet these criteria were considered PT. Cases who were initially diagnosed with PT and met the CPP criteria at follow-up were not included in the study. In addition, cases with missing data, peripheral, and CPP cases with organic pathology detected by cranial/pituitary magnetic resonance imaging were not included in the study. The data of patients diagnosed with CPP and PT were compared.

The study was carried out in accordance with the Declaration of Helsinki Principles and approval was obtained from the Ethics Committee of Hitit University Faculty of Medicine (decision no:194, date: 11.03.2020).

Statistical Analysis

Statistical analyzes in our study were performed using the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normality distribution of the retrospective data was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were presented as mean ± SD in normally distributed data, median (minimum-maximum) in non-normally distributed data, and categorical data as numbers and percentages (%). Student's t-test, Mann-Whitney U test were used to compare groups, and Fisher's Exact chi-square test was used to compare group ratios. It was considered statistically significant when the p value was <0.05. Binary logistic regression analysis was used with the enter method to determine the factors that are effective in the differential diagnosis of CPP and PT.

RESULTS

Sixty-five female patients, 53.8% (n=35) of whom were diagnosed with PT and 46.2% (n=30) with CPP were included in the study. The mean age of the cases was 7.00±0.61 years (5.91-7.90) in patients with PT and 7.19±0.76 years (5.10-7.91) in patients with CPP. There was no statistical difference between them (p=0.285).

While all of the patients diagnosed with PT (n=35) applied with the complaint of breast enlargement, 73.3% of the patients diagnosed with CPP (n=22) had breast enlargement, 16.7% (n=5) had pubic hair growth, and 6.7% (n=2) had pubic and axillary hair growth, 3.3% (n=1) had breast enlargement and pubic hair growth. There was no statistical difference between the two groups in terms of application complaints difference was detected (p=0.001).

The median (median) puberty stage was 2 (2-3) in both groups, and pubic or axillary hair growth was not detected in any of the cases diagnosed with PT. On the other hand, 36.6% (n=11) of the patients with CPP had pubic hair and 26.6% (n=8) had axillary hair. There was no statistical difference between the two groups in terms of puberty stage (p=0.385). The anthropometric features

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of the cases are shown in Table 1, and their laboratory and radiological features are shown in Table 2.

Basal LH level, ovarian volume, height SD value and estradiol level among the parameters used in the differential diagnosis of CPP and PT; Considering the Hosmer and Lemeshow test, it was found to be suitable for logistic regression and statistically significant ($p<0.05$) (Table 3).

DISCUSSION

In our study, our patients with CPP were taller than their peers with PT, had higher LH, FSH and estradiol levels, larger ovarian and uterine volumes, had more advanced bone ages and had higher bone age/calendar age ratios, and the differential diagnosis was the most common and we determined that the most important parameter is the basal LH level. Early recognition of gonadal axis activation will enable early recognition of CPP and PT cases and timely initiation of treatment to ensure adequate height gain in cases with CPP.

Anthropometric measurements are important variables in differentiating central puberty precocious and PT cases. Progression in bone age, increase in growth rate and body weight are expected findings because of sex hormones in CPP cases (11). Kılıç et al. (12) found significantly higher height, weight, and BMI-SD values in CPP cases compared to the PT group. In the study of Çatlı et al. (13), BMI-SD value was found to be twice as high in the CPP group as in the PT group, but the difference was not statistically significant. Similarly, in our study, the BMI-SD value was found to be higher in the group with CPP compared to the group with PT, but no statistical difference was found. In the study of Vurallı et al. (14), patients with CPP had higher bone age, height and BMI SDS at diagnosis than patients with PT. In our study, in accordance with the literature, the height SD value was found to be significantly higher in girls with CPP than in girls with PT. These findings show that anthropometric variables, especially the height SD value, are important clinical findings that support and distinguish the diagnosis when evaluating CPP and PT cases.

Table 1. Anthropometric features of cases diagnosed as premature thelarche and central puberty precox

	Premature telarch (n=35) ($\bar{x}$±SD) (minimum-maximum)	Central pubertal precox (n=30) ($\bar{x}$±SD) (minimum-maximum)	p-value
Age (years)	7.00±0.61 (5.91-7.90)	7.19±0.76 (5.10-7.91)	0.277[1]
Body weight SDS	1.05±0.91 (-1.15-2.53)	1.11±1.07 (-0.87-3.46)	0.821[2]
Height SDS	0.36±0.93 (-1.63-2.11)	1.11±1.26 (-1.32-3.35)	0.008[2]
BMI SDS	0.75±0.87 (-0.92-2.69)	1.11±0.74 (-0.36-2.20)	0.084[2]

[1]Mann-Whitney U test, [2]independent t-test, SD: standard deviation, SDS: standard deviation score, BMI: body mass index, $\bar{x}$: average

Table 2. Laboratory and radiological characteristics of cases diagnosed with premature telarche and central pubertal precox

	Premature telarch (n=35) ($\bar{x}$±SD) (minimum-maximum)	Central pubertal precox (n=30) ($\bar{x}$±SD) (minimum-maximum)	p-value
LH (mIU/mL)	0.36±0.17 (0-0.68)	0.86±1.72 (0.1-9.41)	0.029[1]
FSH (mIU/mL)	2.07±1.46 (0-6.47)	3.2±1.95 (0.2-7.79)	0.008[1]
E_2 (pg/mL)	7.8±3.1 (5-11)	14.8±15.3 (5-60)	0.011[1]
Right ovarian volume (mm^3)	1,204±856 (243-3944)	1,864±1,388 (187-5,040)	0.038[2]
Left ovarian volume (mm^3)	1,198±907 (227-3808)	2,314±2,055 (178-9,090)	0.013[1]
Uterine volume (mm^3)	1,519±882 (346-4,257)	2,585±2,786 (144-12,402)	0.039[1]
Bone age	7.6±0.95 (5-8.83)	8.45±1.04 (5.75-11)	0.003[1]
Bone age/calendar age ratio	1.09±0.12 (0.8-1.4)	1.18±0.16 (0.96-1.3)	0,024[1]

[1]Mann-Whitney U test, [2]independent t-test, SD: standard deviation, $\bar{x}$: average, LH: luteinizing hormone, FSH: follicle stimulating hormone

Today, various hormonal methods such as measurement of basal and stimulated gonadotropin levels are used in the diagnosis of CPP, in addition to clinical findings such as growth rate and advanced bone age. However, there is no diagnostic method that can definitively distinguish CPP from PT (14). Neely et al. (15) evaluated 49 female patients with CPP and found that the diagnostic value of gonadotropin-releasing hormone (GnRH)-stimulated FSH level was low, whereas the basal LH level measured by the third-generation measurement method (ICMA) was more reliable. In the same study, a strong positive correlation was shown between GnRH-evoked LH and basal LH levels (15). In addition, many studies have suggested that baseline LH level can be used in the differential diagnosis of CPP and PT (16-18). In studies evaluating PT and CPP cases in the literature, the baseline LH value was found to be higher in CPP cases than in PT cases (16). Çatlı et al. (13) also found findings supporting this in their study. In a study conducted in our country, in which 344 cases were included, the basal LH level was found to be significantly higher in patients with CPP compared to the group with PT (14). Consistent with the literature, in our study, the basal LH levels of our subjects with CPP were found to be higher than their peers with PT, and the most important parameter used in the differential diagnosis of CPP and PT was the basal LH level. This result supports the knowledge that the basal LH level can be used as a screening test in the diagnosis of CPP.

USG is frequently used for internal genital imaging of girls because of its well-known advantages such as being inexpensive,

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Table 3. Logistic regression analysis of parameters used in the differential diagnosis of central pubertal precox and premature telarche

	Univariate logistic regression						Hosmer and Lemeshow test	
	B	SE	p-value	OR	%95 OR		Chi-square value	p-value
					The lower limit	Upper limit		
Basal LH level	4.158	1.459	0.004	63.9	3.661	1116.728	13.408	0.900
Ovarian volume	1.555	0.719	0.009	4.9	1.856	12.812	9.984	0.712
Height SD value	1.451	0.497	0.013	4.3	1.610	11.314	9.557	0.215
Estrodiol levels	0.181	0.083	0.029	1.2	1.018	1.411	5.188	0.520

S.E: standard error, OR: odds ratio, SD: standard deviation, LH: luteinizing hormone

easily accessible, fast, reliable, reproducible, and noninvasive, and not causing radiation exposure (19,20). The size of the uterus and ovaries, fundo-cervical ratio and endometrial thickness provide detailed information about the size and distribution of ovarian follicles (20). The transformation of the uterus from tubular to bulbous, enlargement in its volume, increase in the corpus/cervix ratio, and the thickening of the endometrium are the symptoms indicating estrogen exposure (21). Haber et al. (22) reported that measurements of uterus and ovarian sizes were useful in distinguishing patients with SPP from patients with PT. In the study of Battaglia et al. (21), it was stated that uterine length and ovarian volumes were increased in patients with SPP. Similarly, in our study, our cases with SPP were found to have larger ovarian and uterine volumes than their peers with PT. In the study of Vurallı et al. (14), although they detected increased uterus and ovarian size on pelvic USG in accordance with advanced pubertal stage in patients with SPP, none of these factors were found to be significant as criteria to be used in the differential diagnosis of SPP and PT in multivariate logistic regression analysis found (14). Della Manna et al. (23) found that bone age was advanced, height and growth rate as well as uterus and ovarian volumes were increased in patients with CPP. In this study, like the study of Vurallı et al. (14), growth rate-SD value was found to be the only important anthropometric finding to be used to differentiate patients with CPP and PT in multivariate regression analyzes. When the order of importance of the parameters used in the differential diagnosis of CPP and PT in our study was determined by logistic regression analysis, the order of importance was determined as basal LH level, ovarian volume, height SD value and serum estradiol level. In conclusion, although various clinical findings can be used in the differential diagnosis of CPP and PT, it is difficult to detect hypothalamic-pituitary-pituitary axis activation based on clinical findings alone (14). The results of our study show that laboratory findings are supportive variables for clinical findings, and the differential diagnosis of CPP and PT should be made by evaluating laboratory and clinical findings together.

Study Limitations

The most important limiting factor of our study is that it was conducted retrospectively. Patients whose data could not be accessed due to insufficient enrollment had to be excluded from the study, and as a result, a limited number of patients could be included in the study.

CONCLUSION

In conclusion, basal LH level is the most important parameter that can be used in demonstrating HPG axis activation and in the diagnosis of SPP in girls presenting with early breast development. Clinical findings such as anthropometric measurements, ovarian and uterine volumes determined by pelvic USG, advanced bone age and increased bone age/calendar age ratio are supportive data that can be used in the differential diagnosis of SPP and PT in addition to laboratory findings. However, it should not be forgotten that laboratory findings are supportive variables and should be evaluated together with clinical findings.

Ethics Committee Approval: The study was carried out in accordance with the Declaration of Helsinki Principles and approval was obtained from the Ethics Committee of Hitit University Faculty of Medicine (decision no: 194, date: 11.03.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - H.N.P.K.; Concept - H.N.P.K.; Design -H.N.P.K.; Data Collection and/or Processing - İ.K.; Analysis and/or Interpretation - H.N.P.K.; Literature Search - H.N.P.K., İ.K.; Writing - H.N.P.K., İ.K.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Çalışma Helsinki İlkeler Deklerasyonu'na uyularak gerçekleştirildi ve Hitit Üniversitesi Tıp Fakültesi Etik Kurulu'ndan onay alındı (karar no:194, tarih: 11.03.2020).

Hasta Onamı: Retrospektif çalışma.

Hakem Değerlendirmesi: Editörler kurulu ve editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazar Katkıları: Cerrahi ve Medikal Uygulama - H.N.P.K.; Konsept - H.N.P.K.; Dizayn - H.N.P.K.; Veri Toplama veya İşleme - İ.K.; Analiz veya Yorumlama - H.N.P.K.; Literatür Arama - H.N.P.K., İ.K.; Yazan - H.N.P.K., İ.K.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

J Acad Res Med 2022;12(1):10-4

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DOI: 10.4274/jarem.galenos.2021.30301
J Acad Res Med 2022;12(1):15-20

The Importance of Radiologic Signs for Giant Lipoma Differentiation From Low-grade Liposarcoma and Its Most Appropriate Surgical Treatment Protocol

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Cite this article as: Sofulu Ö. The Importance of Radiologic Signs for Giant Lipoma Differentiation From Low-grade Liposarcoma and Its Most Appropriate Surgical Treatment Protocol. J Acad Res Med 2022;12(1):15-20

ABSTRACT

Objective: This study aimed to evaluate the importance of preoperative radiologic signs for giant lipoma differentiation from low-grade liposarcoma and reveal the appropriate surgical method.

Methods: This study retrospectively evaluated 59 patients who underwent marginal and wide resection for giant lipomas (21 were females and 15 were males) and low-grade liposarcomas (14 were females and 9 were males). Pre-biopsy radiological signs were investigated using magnetic resonance images. The pre and postoperative functional results were evaluated using the Upper Extremity Functional Index (UEFI), Lower Extremity Functional Index (LEFS), and visual analogue scale (VAS). The functional results were evaluated according to the marginal and wide resection of these lesions.

Results: The preoperative radiologic signs revealed no significant correlations between the thin septa with the giant lipoma or low-grade liposarcoma. However, a significant correlation was determined between the thick septa and globular area with low-grade liposarcoma and homogeneous mass with giant lipoma. Postoperative mid-term UEFI, LEFS, and VAS of the marginal and wide resection were significantly better than the preoperative functional results in both lesions. No differences were found between the preoperative and postoperative mid-term functional results in the marginal and wide resections of either lesion. Local recurrence was detected in four patients with low-grade liposarcoma who underwent marginal resection.

Conclusion: Therefore, thick septa, confluent globular area, and nonadipose mass are distinctive for low-grade liposarcoma, and homogeneous mass is distinctive for giant lipoma. Moreover, it would be more appropriate to treat low-grade liposarcomas with wide surgical resection.

Keywords: Giant lipoma, low-grade liposarcoma, surgical resection, local recurrence, functional results

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Received Date: 01.08.2021 **Accepted Date:** 24.12.2021

J Acad Res Med 2022;12(1):15-20

INTRODUCTION

Lipoma is the most common soft tissue tumor (1). Giant lipomas usually present at a size exceeding 10 cm and a minimum weight of 1,000 g (2). Low-grade liposarcoma is a locally aggressive soft tissue tumor with a tendency toward local recurrence and dedifferentiates to higher grades over time (3).

Significant radiological similarities were found between giant lipoma and low-grade liposarcoma. Some radiological features can help to identify a liposarcoma, such as the size of >10 cm, thick septations, and globular and/or nodular nonadipose areas (4). A significant number of lipomas have an imaging appearance that mimics liposarcoma (5). The literature reported that radiological magnetic resonance (MR)-based studies have difficulties in distinguishing these two tumor types (3,6-9).

Comparative studies on the radiological similarities of these two tumors have been reported in the literature; however, surgical methods and their functional results and complication rates are limited. Marginal or wide resection is recommended in the surgical treatment of giant lipoma and low-grade liposarcoma (10,11). However, the most appropriate surgical method remains controversial. To the best of our knowledge, this is the first comparative study to present the surgical options and their complications and functional outcomes for two different types of tumors.

We hypothesized that these two tumor types will have different radiological signs on MR images and the resection options may differ. This study aimed to evaluate the pre-biopsy radiological features of MR imaging (MRI) in distinguishing giant lipoma and low-grade liposarcoma, as well as evaluate the surgical resection types, complication rates, local recurrence rate, and functional results of marginal or wide resection of giant lipomas and low-grade liposarcomas of the upper and lower extremities.

METHODS

This study was approved by the Marmara University Faculty of Medicine Institutional Review Board (protocol no: 09.2021.811, date: 02.07.2021). All the performed procedures adhered to the ethical rules and principles of the Helsinki Declaration. The patient data were collected from orthopedic oncology notes, clinical records, and imaging systems. This study retrospectively reviewed 67 patients with giant lipomas and low-grade liposarcoma between January 2003 and January 2019. Five patients who were lost to follow-up, one who died because of myocardial infarction (15 months postoperatively) and two who died in a traffic accident were excluded from the study. Patients with metastasis at diagnosis and additional tumoral history were excluded from the study. The remaining 59 patients underwent marginal or wide resection of giant (≥10 cm) lipomas (36 patients; 21 were females, 15 were males) and low-grade liposarcomas (23 patients; 14 were females, 9 were males) were included in the study. The biopsy was performed in all patients before definitive surgery. The same musculoskeletal histopathologist evaluated the specimens. The final pathology in the resected material was compatible with the biopsy results in all patients.

Demographic data of patients were analyzed. The differential diagnosis of the radiological signs as a homogeneous mass, thin septa, thick septa, and the globular area was evaluated via MRI before biopsy (Figure 1-3). A musculoskeletal oncology team, consisting of two orthopedic surgeons, conducted the MRI evaluations and recorded the results in the oncological notes. All MRIs were performed at the same center with the use of a contrast agent. All imaging was performed with 1.5-T magnets (Magnetom Siemens Healthineers, Germany). MR scanning parameters of the T1-weighted SE image are as follows: thickness: 2-5 mm, repetition time (TR): 470-832 ms, and echo time (TE): 7–27 ms. The whole MRI session also included T2-weighted fluid-sensitive, diffusion-weighted, and postcontrast fat-saturated T1-weighted sequences.

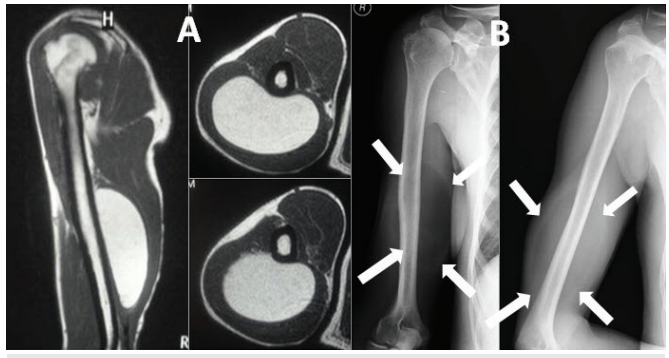

Figure 1. A 44-year-old female patient who had a giant lipoma on her right arm, A) Homogenous mass on MRI, B) Direct radiography gives clues about giant lipomas
MRI: magnetic resonance imaging

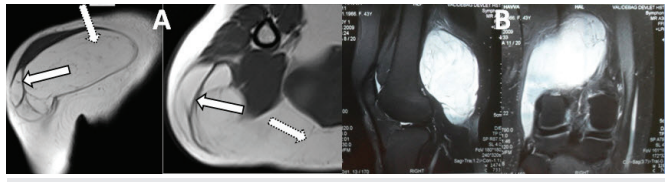

Figure 2. A) A 55-year-old female patient who had low-grade liposarcoma around her shoulder: ⇦ shows thick septa and ⇨ shows thin septa, B) MR images showing liposarcoma in the posterior compartment of the thigh in a 62-year-old man. MR images have pronounced thin septa
MR: magnetic resonance

Marginal or wide resection decision was made following the preoperative biopsy results and radiological signs (10,11). In patients with biopsy results of giant lipoma (n=36), marginal resection (n=26) was performed in the homogenous mass or mild and moderate thin septa and wide resection (n=10) in globular area, moderate and pronounced thick septa, and mild thick septa with moderate or pronounced thin septa. In patients with biopsy results of low-grade liposarcoma (n=23), marginal resection

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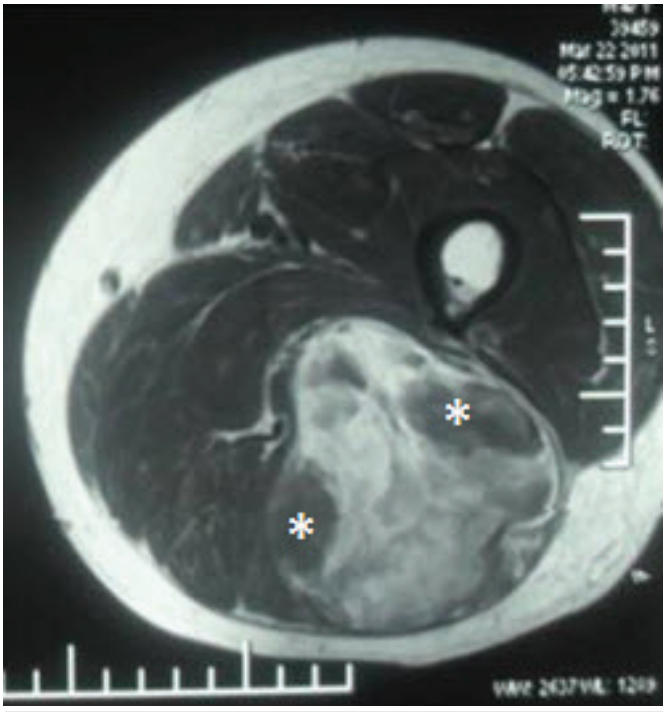

Figure 3. Transverse MR image shows a low-grade liposarcoma in the posterior compartment of the thigh. *confluent globular areas of nonadipose tissue
MR: magnetic resonance

(n=9) was performed in mild and moderate thin septa and wide resection (n=14) in globular area, moderate and pronounced thick septa, and mild, thick septa with moderate or pronounced thin septa.

Patients were followed up at 1, 3, and 12 months postoperatively. Early and late surgical complications, local recurrence, and functional results were compared in the marginal and wide resection. Preoperative and postoperative evaluation of the functional results was conducted using the Upper Extremity Functional Index (UEFI), Lower Extremity Functional Scales (LEFS), and visual analogue scale (VAS) (12,13).

Statistical Analysis

The obtained data in the study were statistically analyzed using the International Business Machines Corporation Statistical Package for the Social Sciences for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using the Wilcoxon rank-sum test, and the χ^2 test for the categorized variables. The Mann-Whitney U test was used to compare the preoperative and postoperative functional outcomes. P-values of <0.05 were accepted as statistically significant.

RESULTS

The comparison of the two groups was made according to the age, sex, average length of follow-up, and lesion location of patients (Table 1). No significant difference was found between the two groups according to the demographic data.

The pre-biopsy radiologic evaluation with the MR images revealed no significant correlation between the presence of thin septa with giant lipomas or low-grade liposarcomas (p=0.133). The presence of homogeneous mass was significantly higher in the giant lipoma group (p<0.0001). The presence of thick septa, confluent globular area, and nonadipose mass were significantly higher in the low-grade liposarcoma group (p<0.0001, p=0.02, p<0.001, respectively) (Table 2).

In the early postoperative period, wound infection was seen in three patients (one marginal and two wide resections) who were diagnosed with giant lipoma, and six patients who were diagnosed with low-grade liposarcoma (one marginal and five wide resections) (Table 3). All infections were managed by intravenous antibiotherapy without any additional interventions. No additional surgical complications were seen in early or late periods.

Marginal resection was performed in 26 giant lipomas and 9 low-grade liposarcomas and wide resection with a thin layer of muscle around the mass in 10 giant lipomas and 14 low-grade liposarcomas. Local recurrence was detected in four patients with low-grade liposarcoma who underwent marginal resection (Table 3).

The postoperative UEFI, LEFS, and VAS scores of the marginal and wide resections were significantly better than the preoperative results in the giant lipoma and low-grade liposarcoma. The differences between the preoperative and postoperative UIEF, LEFS, and VAS scores were insignificant in the marginal and wide resections of both lesions (Table 3).

Table 1. Preoperative demographic evaluation

Factors	Giant lipoma	Low-grade liposarcoma	p
Age	48.5±8.6	51.9±9.8	0.234
Male/female	15/21	9/14	0.846
Average length of follow-up (months)	40.3±15.4	33.3±14.8	0.091
Lesion location			
Upper extremity	9	6	0.925
Lower extremity	27	17	

Table 2. Magnetic resonance signs of two group

MR signs	Giant lipoma n=36	Low-grade liposarcoma n=23	p
⊖Homogeneous mass	19%	0%	<0.0001
⁂Thin septa	0.77±0.63	1.26±0.96	0.133
⁂Thick septa	0.41±0.64	1.69±0.76	<0.0001
⁂Globular area	0.19±0.40	0.82±0.83	0.02
¥Nonadipose mass	2%	11%	<0.001

⊖evaluated as present or absent, ⁂0= absent, 1= mild, 2= moderate, 3= pronounced., ¥evaluated as present or absent, MR: magnetic resonance

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Table 3. The comparison of early-late complication and preoperative and postoperative functional results of both groups according to the surgical excision

	Giant lipoma		p	Low-grade liposarcoma		p
	Marginal resection 26	Wide resection 10		Marginal resection 9	Wide resection 14	
Early wound infection	1	2	0.369	1	5	0.409
Local recurrence	0	0	-	4	0	0.029
Pre-op UIEF	52.0±10.1	47.9±6.4	0.179	41.0±6.1	46.1±6.2	0.107
Post-op UIEF	76.9±3.7	74.8±4.2	0.196	74.3±3.9	72.0±3.7	0.174
Pre-op LEFS	42.8±9.1	48.4±7.5	0.147	39.3±6.4	43.2±8.0	0.269
Post-op LEFS	75.8±4.2	72.7±5.2	0.111	74.4±4.6	72.2±3.7	0.146
Pre-op VAS	4.1±0.9	4.4±0.8	0.404	4.8±1.1	4.7±1.3	0.726
Post-op VAS	0.2±0.4	0.4±0.6	0.680	0.3±0.5	0.6±0.7	0.403

LEFS: Lower Extremity Functional Index, UIEF: Upper Extremity Functional Index, VAS: visual analogue scale

DISCUSSION

Radiological images of giant lipomas and low-grade liposarcomas may show similar features. Additionally, there is no consensus on the most appropriate treatment of these tumors. The current research comprised a comparative study that investigated the preoperative radiological signs and surgical treatment of these tumors. The main findings of this study can be summarized as follows: (a) no significant correlation was found between thin septa with giant lipomas or low-grade liposarcomas; (b) the presence of homogeneous mass was significantly higher in the giant lipoma group; (c) the presence of thick septa, confluent globular area, and nonadipose mass was significantly higher in the low-grade liposarcoma group; and (d) local recurrence was seen at four patients with low-grade liposarcoma who underwent marginal resection.

In giant lipoma and low-grade liposarcoma, most surgeons prefer marginal or wide resection according to the biopsy result (10,11). The experience of the pathologist is significant in the differentiation with biopsy. Contrarily, the differentiation of these two soft tissue masses with biopsy may fail and effective treatments may be delayed. Therefore, preoperative MRI signs and correct histopathological diagnosis are important for surgical resection without tumor cell seeding. Sato et al. (14) analyzed the pathology reports of 637 patients who were operated on with the preoperative diagnosis of lipoma. They reported that eight of these patients had liposarcoma postoperatively. In the current study, histopathological examination of the biopsy and resected specimen was assessed by the same musculoskeletal histopathologist. All of the biopsy results were the same as the final pathological results. Therefore, managing patient with orthopedic oncology with a good team and a multidisciplinary approach are important.

Specific signs with MRI have been reported for two tumors in previous studies (3-8). Thornhill et al. (8) reported that low-grade liposarcoma has more fibrous septa, is more heterogeneous, and contains more nodular or globular areas of nonadipose tissue compared with a lipoma. Pressney et al. (6) demonstrated that lipomas were composed of mature adipocytes that are separated by thin fibrous septa with no significant cytological atypia. Consistent with these studies, significant results were reached with specific MRI signs to differentiate a giant lipoma from low-grade liposarcoma in the current study. The soft tissue mass, which had a homogenous mass and mild, moderate, and thin septa on MRI was diagnosed as giant lipoma. Additionally, the soft tissue mass, which had a globular area and pronounced thick septa on MRI, was diagnosed as low-grade liposarcoma. Shim et al. (3) reported that low-grade liposarcomas are characterized by thick fibrous septa with some small or large blood vessels, and myxoid areas are detected near the septa. According to the current study results, if MR images have isolated pronounced thin septa and isolated thick septa, which can be seen in both giant lipoma and low-grade liposarcoma, a specific distinction cannot be made and a biopsy should be performed for differentiation.

Marginal and wide resection is preferred as a surgical treatment for giant lipoma and low-grade liposarcoma (10,11). However, no acceptable protocols are available that should be used in the surgical treatment for giant lipoma and low-grade liposarcoma. Unlike giant lipoma, low-grade liposarcoma can invade healthy muscles. Additionally, it is usually without a complete tumor capsule (15). Choi et al. (11) reported that marginal resection is sufficient for low-grade liposarcoma although the probability of local recurrence is high. Shim et al. (3) stated that removing the lipomas with marginal resection and low-grade liposarcomas with wide resection is appropriate since local recurrence and dedifferentiation are possible. We believe that wide resection is a more appropriate treatment for low-grade liposarcomas because the possibility of local recurrence and reoperation creates additional morbidity for the patient.

Postoperatively, the local recurrence rate of low-grade liposarcoma is higher than that of giant lipoma (7,11). The primary cause of local recurrence is usually inadequate surgical margins (10). The literature reported that the recurrence rate of lipomas ranged from 3% to 62.5% (9,16,17). Su et al. (18) reported eight patients who underwent wide resection for lipoma, without local

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recurrence. Bassett et al. (19) reported two (4%) recurrences in 55 patients who were diagnosed with an intramuscular lipoma. Choi et al. (11) reported that the local recurrence rate was higher with marginal excision (11.9%) compared with wide excision (3.3%) in low-grade liposarcomas. Consistent with this study, the local recurrence ratio was 44% (4 out of 9) in the low-grade liposarcoma group who underwent marginal resection in the series studies. No local recurrences were found in the low-grade liposarcoma group who underwent wide resection. The incidence of local recurrence was significantly high for the marginal resection group. No local recurrence was observed in the giant lipoma group, in which mass was excised by marginal and wide resection. Therefore, wide resection is the optimal surgical treatment for low-grade liposarcoma (Figure 4).

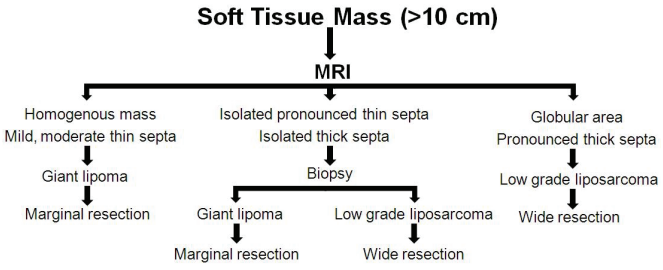

Figure 4. Surgical algorithm of a giant lipomatous tumor
MRI: magnetic resonance imaging

Choi et al. (11) reported no surgery-related infections in their low-grade liposarcoma series. Additionally, Capkin et al. (20) also observed no deep or superficial infection in their lipoma series. Compatible with the literature, no deep infections were observed in the series studied herein. However, superficial wound infections in nine patients were treated with oral antibiotics.

Nishida et al. (16) reported no functional loss in patients with intramuscular lipoma who underwent wide or marginal resections. Contrarily, Capkin et al. (20) stated that severe functional deficits were seen in large or deep-seated locations of the liposarcomas. Arvinius et al. (21) reported that 11 patients with low-grade liposarcoma were managed with marginal excision and they reported a mean Musculoskeletal Tumor Society (MSTS) score of 81.6% at 1 year postoperative. Kito et al. (22) also reported an MSTS score of 98% for the wide resection group in patients with low-grade liposarcoma. Consistent with these studies, the postoperative early 6-month functional results of marginal resection herein were significantly better than the wide resection in both lesions. Additionally, the pain was higher in the first 6 months in the wide resection group than in the marginal resection group in these two soft tissue masses, probably due to the surrounding muscle tissue resection, which can also adversely affect the functional results.

Study Limitations

This study had some limitations. First, it was retrospectively performed with a small number of patients. Hence, the major limitation was the underpowered statistical analysis. However, the radiologic features and surgical experience in a selected patient group were presented. Second, some of the patients had relatively short follow-up periods; however, recurrence can occur after many years. Third, only the differences of these lesions based on the MR images were reported. The utilization of other modalities, such as ultrasound, may provide additional benefits in distinguishing the two tumor types. Finally, functional scores can be biased, as they evaluate only a few functional outcomes, but not the overall health condition and quality of life of patients. Nevertheless, further comparative, long-term studies with larger patient groups are necessary to confirm these findings.

CONCLUSION

Some indications on MR images differentiate a giant lipoma from low-grade liposarcoma. The presence of a homogeneous mass is distinctive for giant lipoma, and thick septa, confluent globular area, and nonadipose mass are distinctive for low-grade liposarcoma on MR images. Local recurrence was seen only in four patients with low-grade liposarcoma who underwent marginal resection. Therefore, considering that low-grade liposarcomas may pose the risk of local recurrence in inappropriate surgery, marginal resection is an improper surgical treatment for low-grade liposarcoma. Wide or marginal resection of both lesions does not adversely affect the functional outcomes, but patients may experience more pain after the wide resection. Multicentric studies with large patient numbers are needed in the literature.

Ethics Committee Approval: This study was approved by the Marmara University Faculty of Medicine Institutional Review Board (protocol no: 09.2021.811, date: 02.07.2021).

Informed Consent: Written consent was obtained from the participants for their records to be included in the study. All data were collected in accordance with the principles of Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma Marmara Üniversitesi Tıp Fakültesi Kurumsal İnceleme Kurulu tarafından onaylanmıştır (protokol no: 09.2021.811, tarih: 02.07.2021).

Hasta Onamı: Kayıtlarının araştırmaya dahil edilmesi için katılımcılardan yazılı onam alındı. Tüm veriler Helsinki Deklarasyonu ilkelerine uygun olarak toplanmıştır.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Finansal Destek: Yazar tarafından finansal destek almadığı bildirilmiştir.

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DOI: 10.4274/jarem.galenos.2021.89421
J Acad Res Med 2022;12(1):21-7

Retrospective Evaluation of Risk Factors for the Development of Invasive Fungal Infections in Immunosuppressed Patients

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Cite this article as: Özalp O, Yeşilkaya A, Akçil Ok M, Arslan AH. Retrospective Evaluation of Risk Factors for the Development of Invasive Fungal Infections in Immunosuppressed Patients. J Acad Res Med 2022;12(1):21-7

ABSTRACT

Objective: The incidence of invasive fungal infection (IFI) is increasing in immunosuppressed patients. Thus, this study aimed to compare the types and the distribution of IFI, determine the probable risk factors in its development, and assess the mortality and underlying diseases among patients with hematological malignancies and those with non-hematological immunosuppression.

Methods: This retrospective study included 84 adult patients with IFI diagnosis between January 1, 2012, and April 1, 2014, at our hospital.

Results: The distribution of cases was documented as follows: 58 (69.0%) patients were proven with IFI, 12 (14.3%) with probable IFI, and 14 (16.7%) with possible IFI. Patient distributions with proven IFI were as follows: 91.4% (53/58) with invasive candidiasis (IC), 5.2% (3/58) with invasive pulmonary aspergillosis (IPA), 1.7% (1/58) with nasopharyngeal invasive fungal involvement, and 1.7% (1/58) with invasive fungal involvement in the colon. All cases of probable and possible IFE (26/26, 100%) were determined as IPA. The following is previously known risk factors for IFI development were evaluated for both groups: immunosuppressive drug usage, renal replacement therapy requirement, mechanical ventilation requirement, presence of a central venous catheter, presence of a urinary catheter, presence of gastrointestinal catheter, mucositis/diarrhea/ileus history, malnutrition, blood product transfusion, bacterial infection, antibacterial treatment, length of hospital and intensive care unit stay, and duration of neutropenia. The immunosuppressive drug usage and neutropenia duration were found to be statistically significant between the hematologic malignancy and non-hematologic immunosuppressive groups. No significant difference was found in other parameters ($p<0.05$).

Conclusion: Our findings followed the literature; however, the mortality in the IC group was found high, similar to the IPA group. Additionally, this study revealed that IFI epidemiology may vary based on the region and the patient. IFIs, which are increasing in frequency, need to be evaluated with a good knowledge of risk factors, using newly developed diagnostic methods, with a multidisciplinary approach.

Keywords: Immunosuppression, invasive fungal infection, risk factors

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Received Date: 01.06.2021 **Accepted Date:** 31.12.2021

J Acad Res Med 2022;12(1):21-7

INTRODUCTION

The epidemiology of fungal infections has changed in recent times. The widespread use of broad-spectrum antibacterial agents and the increasing popularity of fluconazole prophylaxis for controlling Candida albicans infections increased the incidence of filamentous fungal infections (1). Invasive fungal infection (IFI) usually presents as candidemia or invasive aspergillosis, particularly in immunosuppressed patients, such as those with hematological malignancy and solid organ transplant (SOT) recipients (2-4).

Risk factors, such as neutropenia history or corticosteroid or cytotoxic agent consumption, remain important for IFI development (5,6). Today, the risk of IFI in patients without neutropenia is increasing with increasing medical care (7). Therefore, IFI is encountered not only in hematological malignancy, solid cancer, and SOT recipient groups, but also in the immunosuppressed group, such as those with rheumatoid arthritis, chronic renal failure, inflammatory bowel disease, and diabetes mellitus (4,6,8). The presence of predisposing factors, as well as the underlying disorders, is important for IFI developments, which include prolonged hospital or intensive care stay, antibacterial agent administration, serious burn injury, major surgery, malnutrition, and the use of central venous catheter (8).

IFI is a difficult process both in diagnoses and treatments and requires a multidisciplinary approach (9,10). In addition to the comprehensive knowledge of patient risk factors, appropriate and timely usage of microbiological, serological, molecular, and radiological analyses is required for IFI diagnosis. It should be kept in mind that Candida species display different resistance patterns. Therefore, identification at the species level in IFIs is of great importance.

Several studies investigated the development of IFIs in immunosuppressed patients; however, these studies have usually focused on patients with hematological malignancy. Thus, the present study aimed to evaluate the types, distribution, risk factors, and prognosis of IFIs in patients with non-hematological immunodeficiencies, such as solid cancer and SOT recipients, as well as patients with hematological malignancy, and determine the differences between these two groups in terms of risk factors for IFI development.

METHODS

After obtaining approval from the Başkent University Institutional Review Board (decision no: KA14/158, date: 14.05.2014), the present study comprised a total of 84 patients aged ≥18 years, who had been diagnosed with IFI between January 1, 2012, and April 1, 2014, in our hospital. Case identification and classification were performed based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus criteria (5), wherein IFI cases, excluding endemic mycoses, were evaluated in three groups as "proven," "probable," and "possible."

Cases were examined for underlying disorders (hematological malignancy, solid malignancy, and SOT), immunosuppressive therapies (corticosteroid, chemotherapy, T-cell immunosuppressant, etc.), and concomitant systemic diseases. Patients with an absolute neutrophil count of <500/mm^3 in the complete blood count were considered neutropenic. The number of days that patients remained neutropenic, treated as an inpatient, and utilized intensive care service before IFI development was recorded. The presence of mechanical ventilator support, central venous catheter, port, urinary catheter, gastrointestinal catheter, and ostomy (nasogastric catheter, gastrostomy, colostomy, ileostomy, etc.) was also investigated. The history of mucositis, diarrhea, or ileus or blood product transfusions (erythrocyte suspension, thrombocyte suspension, albumin, etc.) before the IFI development was also determined, as well as bacterial infections and antibacterial therapies in the last 3 months before IFI. Patients who require dialysis were considered as patients with renal insufficiency. Malnutrition was assessed based on the serum prealbumin concentration in the last 1 month before the IFI development; those with prealbumin concentration of <14 mg/dL were considered to have malnutrition. The types and agents of IFI were investigated. Thoracic computed tomography was performed for radiological examination of lung involvement in patients with IPA. Galactomannan (GM) antigen was analyzed in all but one IPA patient; the threshold value was predetermined as 0.5. With this, the antifungal treatment of patients was recorded.

Blood culture specimens that were sent to the microbiology laboratory of our hospital were incubated in the BD BACTEC (Becton Dickinson, Sparks, MD, USA) automated blood culture system for 5 days. At the end of this period, the specimens, which grew, were examined under the microscope, and those that formed germ tubes were typed as C. albicans. Those with negative germ tube tests were evaluated by API 20AUX (BioMerieux, Marcyl'Etoile, France) commercial kit. Samples that are taken from sterile body fluids or tissues were cultivated in the Sabouraud dextrose agar, Cornmeal agar, and potato dextrose agar for the fungus, which was named according to the growth time, pigment formation, and microscopic appearance on the preparations with lactophenol cotton blue.

Statistical Analysis

All collected data were transferred to the Statistical Package for the Social Sciences (SPSS®) 19 data system. Continuous variables (age) were presented as mean ± standard deviation, whereas categorical variables (gender, IFI types, immunosuppressant therapy, etc.) were presented as numbers and percentages. The Pearson chi-square test, Yates chi-square test, and Fisher Exact test were used to compare categorical variables between the groups. Data without normal distribution (hospital stay, intensive care stay, and neutropenia duration) were analyzed using the Mann-Whitney U test, which is a nonparametric test to compare outcomes between two independent groups. For all analyses, the level of statistical significance was predetermined as p-values of <0.05.

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RESULTS

This study included 84 immunosuppressed patients, of whom 47 (55.9%) were females and 37 (44.1%) were males. The mean age of patients was 61.4±1.65 (22-88) years. Adult immunosuppressed patients were divided into two groups as hematological (15/84, 17.9%) and non-hematological (69/84, 82.1%) and then were compared. The distribution of patients among the types of IFI according to the EORTC/MSG consensus criteria determined that 58 (58/84, 69.0%) had proven IFI, 12 (12/84, 14.3%) had probable IFI, and 14 (14/84, 16.7%) had possible IFI. Invasive candidiasis (IC) accounted for 91.4% of proven IFI cases (52 candidemia and 1 candidal mediastinitis), whereas IPA accounted for 5.2% (3/58) of this group. Additionally, one of two cases had invasive fungal involvement of the nasopharynx (1/58, 1.7%) and the other case had invasive fungal involvement of the colon (1/58, 1.7%). Spores stained with periodic acid-Schiff were seen in these two cases; however, the agent could not be identified. All probable and possible IFI cases manifested pulmonary aspergillosis (26/26, 100%). The types of IFI according to hematological and non-hematological groups are shown in Table 1. The underlying disorders are presented in Table 2.

The hematological and non-hematological groups were compared in terms of the risk factors, including immunosuppressive therapy, the need for renal replacement therapy and mechanical ventilation, the presence of a central venous, urinary, and gastrointestinal catheter, and history of mucositis, ileus, diarrhea, malnutrition, and blood transfusion. The group comparison in terms of the rate of immunosuppressive therapy administration before developing IFI revealed it to be statistically significantly higher in the hematological malignancy group (15/15, 100%) compared to the non-hematological group (50/69, 72.5%) (p=0.018). No statistically significant difference was determined between the groups, except for receiving immunosuppressive therapy before developing IFI (p>0.05) (Table 3).

The group comparison in terms of 6-month survival following IFI revealed no statistically significant difference between the two groups (p=0.932), (Table 4). The 6-month follow-up period revealed mortality in 37.9% (11/29) of IPA cases and 32.1% (17/53) of IC cases.

Moreover, 75 (89.3%) patients had a bacterial infection before developing IFI (Table 5).

The causative agent was C. albicans in 59% and non-albicans Candida (C. glabrata in 21%, C. tropicalis in 10%, C. parapsilosis in 8%, and C. kefyr in 2%) in 41% of the 53 patients with candidemia (Figure 1).

Antifungal therapies that are performed in the patients were fluconazole in 36 (42.9%), voriconazole in 22 (26.2%), caspofungin in 19 (22.6%), amphotericin B in 4 (4.8%), and anidulafungin in 3 (%3.6) patients, in order. Of the 84 patients, 30 (35.7%) died in 6 months despite appropriate treatment.

GM antigen testing was performed in 29 patients with pulmonary aspergillosis, wherein GM was positive (>0.5) in the serum samples of 6 of 7 (6/7, 85.7%) patients with hematological malignancy and 5 of 22 (5/22, 22.7%) patients with non-hematological malignancy.

No statistical difference was determined between the groups in terms of the mean hospital stay (p=0.301) and intensive care stay (p=0.069) duration; however, the mean duration of neutropenia was statistically significantly longer in the patient group with hematological malignancy vs. the patient group with non-hematological malignancy (p=0.018) (Table 6).

DISCUSSION

The incidence of fungal infections has increased and its epidemiology has changed in the last two decades. Additionally, the incidence of filamentous fungal infections has increased (1). First, infectious disease authorities formed a consensus in 2002 and classified IFIs as proven, probable, and possible (11). Later, they were revised in 2008 and the IFI classification followed the EORTC/MSG consensus criteria. Classification is based on host-related factors, clinical criteria, and mycological criteria. The group that has been repeatedly investigated in IFI studies included patients with hematological malignancies (12-14). SOT recipients and patients with solid cancer are important patient groups for IFI; however, studies with these patient groups are limited. Additionally, studies that compare these two groups are scarce (1,15).

The incidence of candidiasis, with C. albicans as the leading agent, began to decrease in the 1990s, but the incidence of fluconazole-resistant or dose-dependent non-albicans Candida has increased.

The incidence of IFI s, which range from 2% to 49% in patients with hematological malignancy, varies based on the chemotherapy regimen and prophylaxis (13,14,16-19). Many studies revealed that

Table 1. Type of IFI according to hematological and non-hematological groups

	Invasive candidiasis				Pulmonary aspergillosis				Other	Total
	Proven	Probable	Possible	Total (%)	Proven	Probable	Possible	Total (%)	Proven (%)	
Hematological patients	8	-	-	8 (53.3)	-	7	-	7 (46.7)	-	15 (100)
Non-hematological patients	45	-	-	45 (65.2)	3	5	14	22 (31.9)	2 (2.9)	69 (100)
Total	53	-	-	53 (63.1)	3	12	14	29 (34.5)	2 (2.4)	84 (100)

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Table 2. Underlying disorders details in hematological malignancy and non-hematological immunosuppressive patient groups

(n, %)	Underlying disorders (n, %)	n (%)
Hematological malignancy patient groups (15, 17.9%)	AML	5 (5.9%)
	CLL	4 (4.7%)
	CML	3 (3.5%)
	Multiple myeloma	2 (2.3%)
	Lymphoma	1 (1.2%)
Non-hematological immunosuppressive patient groups (69, 82.1%)	Solid cancer (29, 34.5%)	8 (9.5%) over
		5 (5.9%) colon
		3 (3.5%) cervix
		2 (2.3%) endometrioma
		2 (2.3%) peritoneum
		2 (2.3%) breast
		2 (2.3%) pancreas
		1 (1.2%) vagina
		1 (1.2%) prostate
		1 (1.2%) kidney
		1 (1.2%) liver
		1 (1.2%) mesenchymal
	Solid-organ transplantation (20, 23.8%)	9 (10.7%) kidney
		6 (7.1%) heart
		5 (5.9%) liver
	Other (20, 23.8%)	5 (5.9%) CVD
		4 (4.7%) rheumatoid arthritis
		4 (4.7%) kidney failure
		2 (2.3%) heart failure
		1 (1.2%) ulcerative colitis
		1 (1.2%) temporalarteritis
		1 (1.2%) glomerulonephritis
		1 (1.2%) Parkinson's disease
		1 (1.2%) femur fracture operation

AML: acute myeloid leukemia, CLL: chronic lymphocytic leukemia, CML: chronic myeloid leukemia, CVD: cerebrovascular disease

pulmonary aspergillosis was the most common IFI followed by candidemia. A study that evaluated the autopsies of 220 patients with hematological malignancy in the 1990s and 2000s revealed that IPA was the most prevalent with 55-58%. The incidence of Candida infections decreased to 26% in the 2000s from 40% in the 1990s. Contrarily, the incidence of infections caused by Mucorales or Fusarium spp. has slightly increased (12). The present study revealed that 53.3% of the developed IFIs in the hematological group were IC and 46.7% were IPA. Additionally, the finding that primary candidemia accounted for 98% of the IC cases suggests that the difference with the other studies occurred from the higher rate of catheter-related infections in Turkey compared to developed countries.

In patients with hematological malignancy, the most frequently identified risk factors for IC are long-term broad-spectrum antibiotic use, immunosuppression, neutropenia, central venous or arterial catheter, urinary catheter, nasogastric catheter, total parenteral nutrition, mechanical ventilation, renal failure, hemodialysis, splenectomy, steroid use, and long-term (>9 days) intensive care stay (20). The most critical risk factor for developing invasive aspergillosis is deep and prolonged neutropenia. Other risk factors include high-dose corticosteroid or other immunosuppressive therapies, mucosal barrier injury due to cytotoxic chemotherapy, and impaired microbial flora due to broad-spectrum antibiotic use (21). The IPA prevalence among the patients with hematological malignancy is associated with underlying disorders and neutropenia duration, which changes based on the type of chemotherapy (12). The present study revealed a statistically significant duration of neutropenia and immunosuppressive therapy administration (p=0.018 and p=0.018, respectively) for the hematological malignancy group compared to the non-hematological group.

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Table 3. The comparison of hematological malignancies and non-hematological immunosuppressive groups in terms of risk factors

	Hematological malignancy patient groups	Non-hematological immunosuppressive patient groups	p
Immunosuppressive therapy before IFI (+) (n=65)	15	50	0.018
Immunosuppressive therapy before IFI (-) (n=19)	0	19	
Need for renal replacement therapy before IFI (+) (n=21)	2	19	0.335
Need for renal replacement therapy before IFI (-) (n=63)	13	50	
Mechanical ventilation before IFI (+) (n=29)	2	27	0.074
Mechanical ventilation before IFI (-) (n=55)	13	42	
Central venous catheter before IFI (+) (n=60)	10	50	0.892
Central venous catheter before IFI (-) (n=24)	5	19	
Urinary catheter before IFI (+) (n=56)	11	45	0.763
Urinary catheter before IFI (-) (n=28)	4	24	
Gastrointestinal catheter before IFI (+) (n=19)	2	17	0.502
Gastrointestinal catheter before IFI (-) (n=65)	13	52	
History of mucositis, ileus, diarrhea (+) (n=30)	5	25	0.932
History of mucositis, ileus, diarrhea (-) (n=54)	10	44	
Malnutrition before IFI (+) (n=24)	2	22	0.212
Malnutrition before IFI (-) (n=60)	13	47	
Blood transfusion before IFI (+) (n=40)	6	34	0.713
Blood transfusion before IFI (-) (n=44)	9	35	

IFI: invasive fungal infections

Table 4. Six-month survival after IFI (n= patients)

	6-month survival after IFI		Total (n=84)	p
	Alive (n=21)	Ex (n=63)		
Hematological malignancy patient groups	9	6	15	0.932
Non-hematological immunosuppressive patient groups	45	24	69	
Total	54	30	84	

IFI: invasive fungal infections

The incidence of IFI in SOT recipients, who account for the substantial proportion of the non-hematological immunosuppressed group, changes based on the transplanted organ. A 5-year prospective study conducted by The Transplant Associated Infection Surveillance Network with 23 transplantation centers from the United States of America the following cumulative incidence of IFI according to the transplanted organs: small intestine in 11.6%, lung in 8.6%, liver in 4.7%, heart in 4%, pancreas in 3.4%, and kidney in 1.3%. The most common IFIs in order of decreasing prevalence were IC in 53%, invasive aspergillosis in 19%, and cryptococcosis in 8% (3). Another prospective study revealed that Candida is the most common agent pathogen of the IFIs, excluding lung transplantation, and IPA was the agent most frequently reported after lung transplantation (22). The present study revealed that IC dominated the entire non-hematological group, but specific to the SOT recipients, wherein pulmonary aspergillosis accounted for 75% and candidemia accounted for 25% considering 9 renal, 6 heart, and 5 liver transplant recipients. In the literature, IFI was most commonly determined in the form of pulmonary aspergillosis in the heart and liver transplant recipients and the form of IC in the liver and kidney transplant recipients (3,22,23). The present study revealed that pulmonary aspergillosis was determined in five of the six (5/6, 83.3%) heart transplant recipients, which was higher compared to the liver and kidney transplant recipients, consistent with the literature (22).

Statistically significantly different parameters between the groups include neutropenia duration and immunosuppressive therapy administration, which were determined in the hematological group (1). Other parameters, such as the need for renal replacement therapy, need for mechanical ventilation, and the presence of a central venous catheter, posed similar risks for the hematological and non-hematological groups.

The literature reported a crude mortality rate increasing up to 60% (16-19) after IFI. The present study revealed a 35.7% overall crude mortality rate (for 6 months after IFI). However, the crude mortality rate was 40% for the hematological malignancy group

Table 5. Recent bacterial infections before IFI

	Bacteremia	Pneumonia	İntra abdominal	Urinary system	Febrile neutropenia	Complicated soft tissue infection	None
Hematological malignancy patient groups (n=15)	1 (6.7%)	5 (33.3%)	0	4 (26.7%)	5 (33.3%)	0	0
Non-hematological immunosuppressive patient groups (n=69)	14 (20.3%)	30 (43.5%)	6 (8.7%)	6 (8.7)	1 (1.5%)	3 (4.3%)	9 (13.0%)
Total (n=84)	15 (17.9%)	35 (41.7%)	6 (7.1%)	10 (11.9%)	6 (7.1%)	3 (3.6%)	9 (10.7%)

IFI: invasive fungal infections

and 34.8% for the non-hematological group, which were similar to the limited number of studies in the literature (1,15). These data suggest that IFIs are very serious and are used to determine the prognosis not only in the hematological group but also in the non-hematological group. The evaluation of the mortality according to the agent pathogens revealed no difference between the IPA and IC. Determining the association of crude mortality rates with fungal infections is impossible; however, a high mortality rate in the patients who develop IC is inconsistent with the literature and is striking (1).

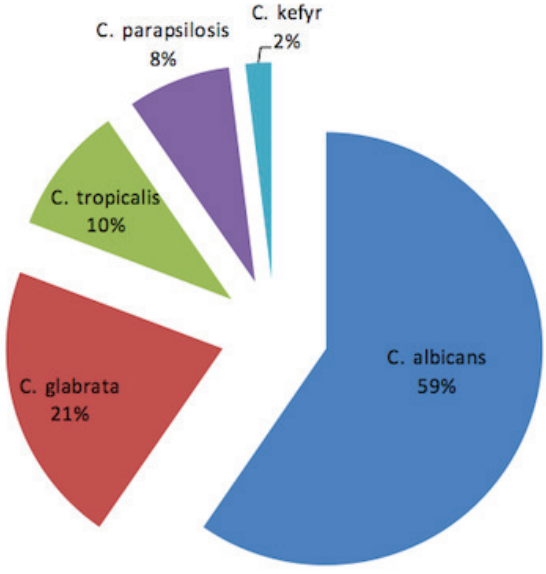

Figure 1. Range of Candida species

The present study revealed consistent GM antigen testing results with the literature and suggest that serum GM has limited diagnostic value, particularly in the non-hematological group (24).

The multicenter study published in 2009 revealed that fungi account for 19%, and Candida spp. account for 18.5% of the culture-positive circulatory system infections (23). The present study revealed 59% C. albicans and 41% non-albicans Candida of the candidemia, which was determined to be the most common type of IFI. Therefore, C. albicans remains the leading cause of candidemia with non-albicans Candida having considerable prevalence.

Study Limitations

The limitations of our study are its retrospective nature and the low number of our cases as 84. Multi-center studies on a much larger number of cases will significantly contribute to this issue.

CONCLUSION

Our findings are following the literature, but the high mortality rate in patients with IC drives attention. This study also revealed that the epidemiology of IFI may vary based on the region and the patient. A better understanding of the risk factors of common sensed IFIs is necessary, as well as maintaining the extensive usage of newly developed diagnostic methods and multidisciplinary approaches.

Ethics Committee Approval: This study obtaining approval from the Başkent University Institutional Review Board (decision no: KA14/158, date: 14.05.2014).

Informed Consent: Retrospective study.

Table 6. Mean hospital stay, mean ICU stay, and mean duration of neutropenia before IFI (days) [mean/median (minimum-maximum)]

	Hematological malignancy patient groups	Non-hematological immunosuppressive patient groups	Overall average	p
Mean hospital stay before IFI (days)	19.7/16.0 (3-64)	37.8/22.0 (0-360)	34.6/18.0 (0-360)	0.301
Mean ICU stay before IFI (days)	2.8/0.0 (0-16)	9.7/4.0 (0-51)	8.4/1.0 (0-51)	0.069
Mean duration of neutropenia before IFI (days)	7.1/0.0 (0-30)	2.5/0.0 (0-30)	3.3/0.0 (0-30)	0.018

IFI: invasive fungal infections, ICU: intensive care unit

J Acad Res Med 2022;12(1):21-7

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - O.Ö.; Concept - O.Ö., A.Y., A.H.A.; Design - O.Ö., A.Y., A.H.A.; Data Collection and/or Processing - O.Ö., M.A.O.; Analysis and/or Interpretation - O.Ö., A.Y., M.A.O., A.H.A.; Literature Search - O.Ö., A.Y.; Writing - O.Ö.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma Başkent Üniversitesi Kurumsal İnceleme Kurulu'ndan onay almıştır (karar no: KA14/158, tarih: 14.05.2014).

Hasta Onamı: Retrospektif çalışma.

Hakem Değerlendirmesi: Editörler kurulu ve editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazar Katkıları: Cerrahi ve Medikal Uygulama - O.Ö.; Konsept - O.Ö., A.Y., A.H.A.; Dizayn - O.Ö., A.Y., A.H.A.; Veri Toplama veya İşleme - O.Ö., M.A.O.; Analiz veya Yorumlama - O.Ö., A.Y., M.A.O., A.H.A.; Literatür Arama - O.Ö., A.Y.; Yazan - O.Ö.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

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DOI: 10.4274/jarem.galenos.2022.44127
J Acad Res Med 2022;12(1):28-35

COVID-19 Vaccination Practice of Children with Rheumatic Disease: A Survey-based Study

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Cite this article as: Yıldız M, Haşlak F, Günalp A, Adrovic Yıldız A, Şahin S, Barut K, Kasapçopur Ö. COVID-19 Vaccination Practice of Children with Rheumatic Disease: A Survey-based Study. J Acad Res Med 2022;12(1):28-35

ABSTRACT

Objective: This cross-sectional study was carried out to investigate the vaccination status of children with rheumatic disease and the reasons why children were not vaccinated.

Methods: In November 2021, a web-based questionnaire was shared with the families of patients who were over 12 years. The families were asked about the socio-demographic features and the reasons for not vaccinating.

Results: A total of 160 patients (90 females) were eligible for the study. The median age was 14.9 (12-17.9) years. The study group comprised 94 patients with autoinflammatory diseases, 43 patients with juvenile idiopathic arthritis, 18 patients with connective tissue diseases, and 5 patients with vasculitis. The parent-reported vaccination rate was 75% in our patient group. The median children age, the median parental age and parental vaccination rates were lower in unvaccinated patients (for all p-value <0.05). In this study, the most common reasons for not vaccinating children with rheumatic disease were fear of vaccine side effects, not-decided-yet, and concerns related to underlying rheumatic disease and medications used. There was no difference between the groups according to patient gender, diagnosis, and medications they were on. Similarly, education levels of the parents and employment status were comparable between the groups (for all p-value >0.05).

Conclusion: These results, together with the results of previous studies, may provide clues to governments and health authorities to understand the drivers of vaccine hesitancy and help increase the coverage of vaccination programs.

Keywords: Vaccine, COVID-19, hesitancy, rheumatic, children

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Received Date: 13.01.2022 **Accepted Date:** 25.01.2022

J Acad Res Med 2022;12(1):28-35

INTRODUCTION

A novel infectious disease named coronavirus disease-2019 (COVID-19) was defined in late 2019, after the isolation of a new coronavirus variant of severe acute respiratory syndrome coronavirus-2, from the patients who had contact with the same animal market and subsequently developed lower respiratory tract infection (1,2). The disease spread all over the world in a short time and became a pandemic. According to the World Health Organization (WHO) coronavirus dashboard, it caused 5,446,753 deaths world-wide by 5th January 2022 (3). Apart from its effects on public health, the disease has massively affected nearly all aspects of social and economic activities globally since the first case was reported, and its negative effects on daily life are still ongoing.

Although more than 2 years have passed since the identification of the disease, an effective treatment could not be developed for COVID-19. Therefore, social distance, face masks, personal hygiene, and vaccination are still of vital importance for preventing the disease. According to the report of WHO, currently, 331 vaccine products (194 are in the pre-clinical phase and 137 are in clinical trials) are under development (4). Studies regarding the efficacy and safety of COVID-19 vaccines in children and adolescents are increasing day by day, and early results show that many vaccines are effective and safe. In the light of current information, the American Academy of Pediatrics recommends that children and adolescents aged 5 years and older, who have no contraindications for COVID-19 vaccination, should be vaccinated with a vaccine approved for their age (5-9). Even though many studies have shown that the mortality and morbidity of COVID-19 in children is lower than in adults, vaccination of children is of great importance in order to control the pandemic as they may cause the spread of the disease (10,11). Therefore, many countries have included children of various age groups in their COVID-19 immunization programs. In Turkey, children older than 12 with chronic medical conditions have been being vaccinated since August 2021.

Although great progress has been made worldwide with COVID-19 vaccine programs, vaccine hesitancy, which is defined by WHO as a delay in the acceptance of the vaccine or the refusal to be vaccinated despite the possibility of accessing the vaccine, is increasing all over the world and has reached dimensions that may threaten public health and WHO listed vaccine hesitancy among the top 10 global health threats in 2019 (12-14). Therefore, it is essential to investigate the vaccination rates of the patients and the attitude of the parents against the vaccine to expand the scope of the vaccination programs.

This cross-sectional study was carried out to investigate the vaccination status of children with rheumatic disease followed in our center, and the reasons why children are not vaccinated for non-vaccinated ones.

METHODS

Study Group

In November 2021, a web-based questionnaire was prepared in Google Forms platform and shared with the families of patients who had been followed up at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Department of Pediatric Rheumatology. In this form, the families were asked about the socio-demographic features (parental education, employment status, monthly income, COVID-19 vaccination status, household size), the children's diagnosis, medication history, follow-up duration and vaccination status. Additional questions to the families of unvaccinated children were asked about the reasons for not vaccinating.

In our country, children under the age of 12 years with chronic medical conditions were started to be vaccinated in August 2021 and the children with rheumatologic disease have been vaccinated since then. Currently, there is no vaccination program against COVID-19 for children under the age of 12 years in Turkey. Therefore, children with rheumatological diseases aged between 12 and 18 years and whose families volunteered to participate in the study were included in the study. An informed consent was obtained from the patients in the questionnaire, and patients who did not want to participate were excluded from the study.

Statistical Analysis

All of the statistical analyses were done by using IBM SPSS 21.0 program (SPSS Inc., Chicago, IL, USA).

Categorical variables were presented as numbers (percentages) and continuous variables as mean ± standard deviation or median (minimum-maximum) depending on their distribution. The distribution of the continuous data was checked by the Kolmogorov-Smirnov test and/or Shapiro-Wilk tests. The comparison of the categorical variables was performed with the chi-square test. While continuous variables with normal distribution were compared with the Student's t-test, those without normal distribution were compared by using the Mann-Whitney U test. The p-value <0.05 was considered significant.

Ethics

The study and its protocol were reviewed and approved by İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Institutional Review Board (decision no: 179227, date: 10.09.2021).

RESULTS

Baseline Characteristics and Demographic Features

After the survey was circulated, 402 participants fulfilled the survey. After the exclusion of duplicate entries (n=16), entries of the patients who were younger than 12 years of age (n=152) and were older than 18 years of age (n=71), and those who improperly filled entries (n=3); a total of 160 patients (90 females) were eligible for the study.

The median age was 14.9 (12-17.9) years, and the median follow-up duration was 8 (0.7-17) years. The study group comprised of 94 patients with autoinflammatory diseases [Familial Mediterranean fever (FMF): 91, hyperimmunoglobulin D syndrome (HIDS): 2, cryopyrin associated periodic syndrome: 1], 43 patients with

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juvenile idiopathic arthritis (JIA), 18 patients with connective tissue diseases [systemic lupus erythematosus (SLE): 13, dermatomyositis: 4, scleroderma: 1), and 5 patients with vasculitis (deficiency of adenosine deaminase-2 (DADA-2): 2, Behçet's disease (BD): 1, granulomatous polyangiitis: 1, Kawasaki disease (KD): 1].

Of 160 patients, 90 (56.3%) were using colchicine. While 33 patients were on conventional disease modifying anti-rheumatic drugs (cDMARDs) (methotrexate: 17, hydroxychloroquine: 8, mycophenolate mofetil: 8, cyclosporin A: 4, azathioprine: 3, sulfasalazine: 2, leflunomide: 1), 35 patients were under biologic disease modifying anti-rheumatic drugs (bDMARDs) (etanercept: 11, canakinumab: 11, adalimumab: 8, tocilizumab: 4, anakinra: 2). Baseline characteristics of the study group are presented in Table 1.

COVID-19 Vaccination Status of the Patients

The Ministry of Health of the Republic of Turkey started to vaccinate children over the age of 12 years with chronic diseases against COVID-19 in August 2021. Since then, all of our patients over the age of 12 years with rheumatological disease can be vaccinated. As the patients under 12 years of age were excluded from the study, all of the participants were within the scope of the COVID-19 vaccination program.

The overall parent-reported COVID-19 vaccination rate in our patient group was 75% and 40 patients with rheumatologic conditions (FMF: 24, JIA: 10, SLE: 2, HIDS: 1, BD: 1, KD: 1, DADA-2: 1) had not been vaccinated. Maternal and paternal COVID-19 vaccination rate among our patient group was 86.9% and 90.6%, respectively (Table 1).

Reasons Why Children are not Vaccinated

As it is presented in Table 2, the most common reason for children not being vaccinated was the fear of side effect, which was pointed out by 20 (50%) of the subjects. Of these parents, only 9 (22.5%) stated that they knew/heard someone around them had experienced side effects after COVID-19 vaccination. Other main reasons mentioned by parents were their children's having rheumatic disease (25%) and using immunosuppressive drugs (25%). A total of 8 (25%) of subjects specified the vaccine being produced abroad as a reason. When these subjects were asked if a kind of COVID-19 vaccine would be produced in Turkey, whether they would vaccinate their children; only 1 (12.5%) parent answered as "yes", 1 (12.5%) answered as "no", and 6 (75%) answered as "not sure". Disbelief in efficacy of the vaccine and disbelief in existence of coronavirus were pointed out as reasons by 5 (12.5%) and 1 (2.5%) of the parents. In addition, 5 (12.5%) mentioned that they were trying to protect their children naturally (herbal medicine, etc.) instead of vaccination. Ten (%25) parents stated that they had not decided yet.

Comparison of the Baseline Characteristics According to Vaccination Status

While the median age [15 (12-17.9) years vs. 14.6 (12-17.7) years; p-value: 0.02], maternal age [41 (32-57) years vs. 39 (33-50) years; p-value: 0.004] and paternal age [45 (33-71) years vs. 42 (36-56)

Table 1. Socio-demographic characteristics of the study group

	n (%) or median (minimum-maximum)
Number of patients	160 (100)
Gender (females, %)	90 (56.3)
Age (years)	14.9 (12-17.9)
Diagnosis n (%)	
Autoinflammatory diseases	94 (58.8)
Familial Mediterranean fever	91(56.9)
Hyperimmunoglobulin D syndrome	2 (1.3)
Cryopyrin associated periodic syndrome	1 (0.6)
Juvenile idiopathic arthritis	43 (26.9)
Connective tissue diseases	18 (11.3)
Systemic Lupus Erythematosus	13 (8.1)
Dermatomyositis	4 (2.5)
Scleroderma	1 (0.6)
Vasculitis	5 (3.1)
Deficiency of adenosine deaminase 2	2 (1.3)
Behçet's disease	1 (0.6)
Granulomatous polyangiitis	1 (0.6)
Kawasaki disease	1 (0.6)
Median follow-up duration (years)	8 (0.7-17)
Medications n (%)	
Colchicine	90 (56.3)
Methotrexate	17 (10.6)
Canakinumab	11 (6.9)
Etanercept	11 (6.9)
Hydroxychloroquine	8 (5)
Adalimumab	8 (5)
Tocilizumab	4 (2.5)
Mycophenolate mofetil	4 (2.5)
Cyclosporin A	4 (2.5)
Acetylsalicylic acid	4 (2.5)
Azathioprine	3 (1.9)
Sulfasalazine	2 (1.3)
Anakinra	2 (1.3)
Leflunomide	1 (0.6)
Maternal characteristics	
Median age (years)	41 (32-57)
Education	
Less than high school	59 (36.9)
High school	63 (39.4)
More than high school	38 (23.8)
Employment status	
Unemployed	113 (70.7)
Employed	47 (29.3)

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COVID-19 vaccination status Vaccinated Not vaccinated	 139 (86.9) 21 (13.1)
Paternal characteristics	
Median age (years)	44 (33-71)
Education Less than high school High school More than high school	 64 (40) 49 (30.6) 47 (29.4)
Employment status Unemployed Employed	 32 (20) 128 (80)
COVID-19 vaccination status Vaccinated Not vaccinated **Household**	 145 (90.6) 15 (9.4) 4 (2-7)
Family monthly income	
<500$	75 (46.9)
500-1,000$	55 (34.4)
1,000-2,000$	23 (14.4)
2,000-3,000$	4 (2.5)
>3,000$	3 (1.9)
Patient's childhood vaccination status	
Vaccinated	154 (96.3)
Not vaccinated	6 (3.8)
Patient's COVID-19 vaccination status	
Vaccinated	120 (75)
Not vaccinated	40 (25)

COVID-19: coronavirus disease-2019

Table 2. Reasons why the patients are not vaccinated

	n (%)
I am afraid of the side effects.	20 (50)
I have not decided yet.	10 (25)
My child is on immunosuppressive drug.	8 (20)
My child has a rheumatologic disease.	8 (20)
The vaccine was produced abroad.	8 (20)
I do not believe in the efficacy of the vaccine.	5 (12.5)
I am trying to protect my children naturally (herbal medicine, etc.).	5 (12.5)
I do not believe in coronavirus.	1 (2.5)

years; p-value: 0.004] were higher in the vaccinated patient group, the median follow-up duration [7 (0.7-17) years vs. 10 (3-15) years; p-value: 0.015] was lower than in non-vaccinated ones.

A total of 98.3% of COVID-19 vaccinated subjects and 90% of non-vaccinated children were vaccinated appropriately according to national immunization program (p-value =0.01). Similarly, among vaccinated ones, maternal (95% vs. 62.5%) and paternal COVID-19 vaccination rates (95% vs. 77.5%) were higher than in the non-vaccinated group (both p-value <0.001).

The rate of the patients with a family income lower than 500$ was lower in the vaccinated patient group [48 (40%) vs. 27 (67.5%)] and the rate of the patients with a family income between 500$ and 1,000$ was higher in the vaccinated patient group than in the non-vaccinated patient group [48 (40%) vs. 7 (17.5%); p-value: 0.02].

While family history of COVID-19 among the first-degree relatives of the patients was lower in the vaccinated patient group than in the non-vaccinated patient group [52 (43.3%) vs. 25 (62.5%); p-value: 0.03], there was no difference between the groups according to COVID-19 related deaths among the first-degree relatives of the patients (p-value: 0.56).

There was no difference between the groups in terms of patient gender, diagnosis, and medications they were on. Similarly, education levels of the parents and employment status were comparable between the groups (for all p-value >0.05). All of the comparisons were represented in Table 3 and Figure 1.

DISCUSSION

In this cross-sectional study, we presented a parent-reported 75% vaccination rate in children with rheumatic disease over 12 years of age and a lower median age, lower parental age, and lower parental COVID-19 vaccination rate in unvaccinated patients. In addition, the most common reasons for not vaccinating children with rheumatic disease in this study were the fear of vaccine side effects, having not decided yet, and concerns related to underlying rheumatic disease and medications used.

In our study group, the parent-reported vaccination rate among children with rheumatic disease over 12 years of age was 75%. As of 7th January 2022, according to the European Centre for Disease Prevention and Control, the median cumulative uptake of at least one vaccine dose in the member states of the European Union was 32% for children between the ages of 10 and 14 years and 71.6% for children between the ages of 15 and 17 years (15). On the report of Ministry of Social Affairs and Health of France, it was stated that 82% of children between the ages of 12 and 17 years received at least one dose of COVID-19 vaccine and it was given as 60.8 % by the Federal Ministry of Health of Germany for children in the same age group (16,17).

To our knowledge, there are no exact data for Turkey and any other country on COVID-19 vaccine coverage among children with rheumatological diseases. There are only a few studies in the literature on the acceptance of a potential COVID-19 vaccine among adult patients with rheumatic diseases, which were usually conducted before or shortly after massive vaccination programs had launched. In these studies, conflicting reports were reported regarding the attitudes of rheumatology patients towards potential vaccines. While some studies reported a lower rate of acceptance of a potential COVID-19 vaccine among patients with rheumatic diseases than control groups, other studies reported a similar rate of intention to be vaccinated against COVID-19 in patients with rheumatic diseases and control groups (18-21). It has been shown that vaccine acceptance rates can change over

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Table 3. Comparison of vaccination status of the patients according to demographic features

	Vaccinated (n=120)	Not vaccinated (n=40)	p-value
Gender (females, %)	69 (57.5)	21 (52.5)	0.58
Age (years)	15 (12-17.9)	14.6 (12-17.7)	0.02
Diagnosis n (%)			
Autoinflammatory diseases	69 (57.5)	25 (62.5)	0.15
Juvenile idiopathic arthritis	33 (27.5)	10 (25)	
Connective tissue diseases	16 (13.3)	2 (5)	
Vasculitis	2 (1.7)	3 (7.5)	
Follow-up duration (years)	7 (0.7-17)	10 (3-15)	0.015
Medications n (%)			
Colchicine	65 (54.2)	25 (62.5)	0.35
Methotrexate	15 (12.5)	2 (5)	0.18
Canakinumab	9 (7.5)	2 (5)	0.58
Adalimumab	7 (5.8)	1 (2.5)	0.40
Hydroxychloroquine	6 (5)	2 (5)	1.00
Etanercept	6 (5)	5 (12.5)	0.10
Tocilizumab	2 (1.7)	2 (5)	0.24
Mycophenolate mofetil	3 (2.5)	1 (2.5)	1.00
Cyclosporin A	4 (3.3)	0 (0)	0.24
Acetylsalicylic acid	3 (2.5)	1 (2.5)	1.00
Azathioprine	3 (2.5)	0 (0)	0.31
Sulfasalazine	2 (1.7)	0 (0)	0.41
Anakinra	2 (1.7)	0 (0)	0.41
Leflunomide	1 (0.8)	0 (0)	0.56
Maternal characteristics			
Median age (years)	41 (32-57)	39 (33-50)	0.004
Education Less than high school High school More than high school	 41 (34.2) 47 (39.2) 32 (26.7)	 18 (45) 16 (40) 6 (15)	0.26
Employment status Unemployed Employed	 82 (67.5) 39 (32.5)	 32 (80) 8 (20)	0.13
COVID-19 vaccination status Vaccinated Not vaccinated	 114 (95) 6 (5)	 25 (62.5) 15 (37.5)	<0.001
Paternal characteristics			
Median age (years)	45 (33-71)	42 (36-56)	0.004
Education Less than high school High school More than high school	 47 (39.2) 38 (31.7) 35 (29.2)	 17 (42.5) 11 (27.5) 12 (30)	0.87
Employment status Unemployed Employed	 23 (19.2) 97 (80.8)	 9 (22.5) 31 (77.5)	0.64
COVID-19 vaccination status Vaccinated Not vaccinated	 114 (95) 6 (5)	 31 (77.5) 9 (22.5)	0.001
Household	4 (2-7)	4 (3-7)	0.06
Family monthly income			
<500$	48 (40)	27 (67.5)	0.02
500-1,000$	48 (40)	7 (17.5)	
1,000-2,000$	17 (14.2)	6 (15)	
2,000-3,000$	4 (3.3)	0 (0)	
>3,000 $	3 (2.5)	0 (0)	
Patient's childhood vaccination status			
Vaccinated	118 (98.3)	36 (90)	0.01
Not vaccinated	2 (1.7)	4 (10)	
Has anyone in the family had COVID-19?			
No	68 (56.7)	15 (37.5)	0.03
Yes	52 (43.3)	25 (62.5)	
Has anyone in the family died due to COVID-19?			
No	119 (99.2)	40 (100)	0.56
Yes	1 (0.8)	0 (0)	

COVID-19: coronavirus disease-2019

time and there are differences between the time periods of the mentioned studies (22). This makes it difficult to compare the rates reported in studies with each other. Therefore, it would be more plausible to focus on the reasons for vaccine hesitancy and the demographics of vaccine hesitant patient population rather than acceptance rates.

The comparisons between vaccinated and non-vaccinated patients showed that the median age of the non-vaccinated patients was lower than that of the vaccinated patients. In accordance with our results, Verger et al. (23), in their study conducted with French adult population to assess their attitudes toward COVID-19 vaccination acceptance for children and adolescents, found that the COVID-19 vaccine acceptance rate of the participants was highest for adolescents (62.7%) and lowest for children under the age of 6 years (31%). Similarly, Goldman et al. (24) reported that a higher intention to vaccinate children is related to children being older. Another significant finding of our study is the median parental age of vaccinated patients being higher than that of non-vaccinated patients. There are several studies on parents'/caregivers' intentions to vaccinate their children against COVID-19 in the literature and one of the most frequently reported factors influencing parental attitudes in these studies is parental age (5). In vast majority of these studies, similar to our findings, it was reported that older parents tended to have positive attitude towards COVID-19 vaccination for their children (24-29).

In our study group, maternal and paternal vaccination rates against COVID-19 were higher among vaccinated children than in the non-vaccinated group. These results support the findings of previous studies reporting that the parents who wanted to vaccinate

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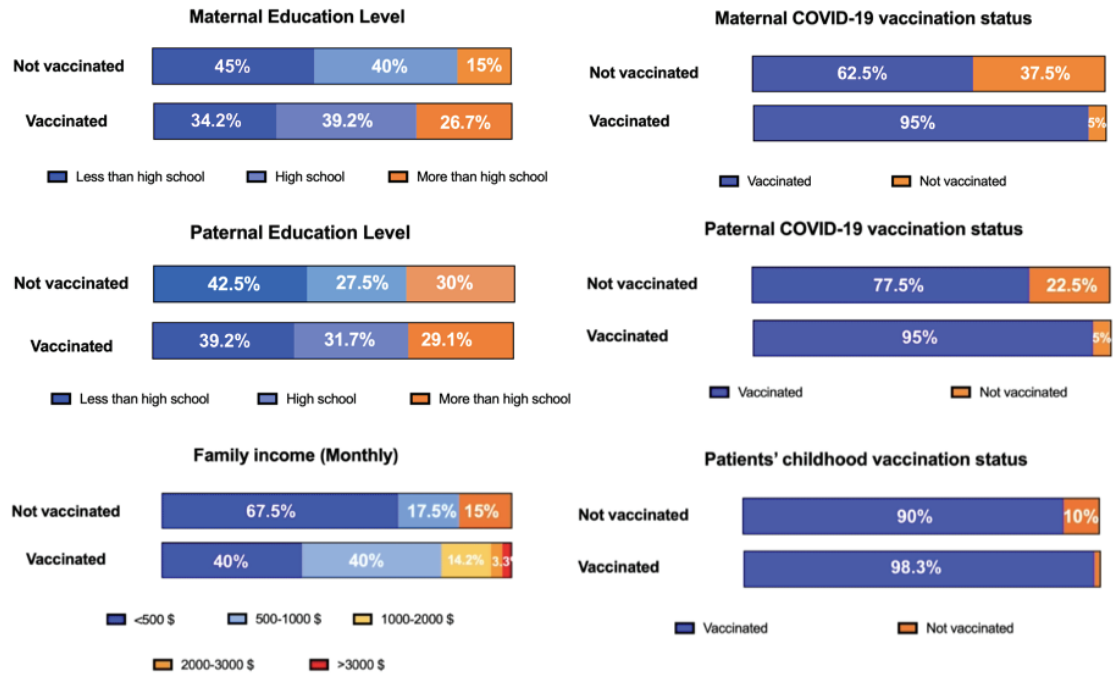

Figure 1. Baseline characteristics according to COVID-19 vaccination status of children
COVID-19: coronavirus disease-2019

themselves against COVID-19 were more likely to vaccine their children (27,30,31). In addition to these, not surprisingly, the rates of children who were vaccinated appropriately according to national childhood immunization program among COVID-19 vaccinated subjects were higher than those of the remaining children. It is shown in the previous studies that the parents who had got influenza vaccine in the previous season were more reluctant to vaccine themselves and their children against COVID-19 (24,26,32,33). In addition, Skjefte et al. (34) reported that one of the main predictors of the COVID-19 vaccine acceptance was confidence in childhood vaccination. These findings were further supported by other studies (35,36). Contrary to these reports, Yılmaz and Sahin (27) found no association between parental willingness to have their children vaccinated and routine vaccination. Yet, in the same study, the authors reported that the parents whose children had received paid-for vaccines were more reluctant to allow their children to receive COVID-19 vaccine (27). These findings suggest that the unwillingness of parents to vaccinate their children against COVID-19 is not only specific to COVID-19 vaccine, but also associated with general opposition to vaccination. On the other hand, 90% of the non-vaccinated children in our study were vaccinated appropriately according to national childhood immunization program. It is more likely that the parents of patients in this group did not allow their children to be vaccinated against COVID-19 because of COVID-19 vaccine-specific concerns rather than general vaccine refusal. Thus, it will be beneficial for health authorities to analyze these parental profiles in detail and to develop strategies specific to these profiles for increasing the success and coverage of the vaccination program.

In our study, the top reason for rejecting COVID-19 vaccination for children with rheumatic disease was the fear of vaccine side effects, which was also reported as the most common reason for unwillingness to vaccinate children in several studies (5,24,27,30,32,34,37). Other reasons mentioned by the parents were concerns related to underlying rheumatic disease and medications used. In addition to these, 12.5% of the parents whose children were not vaccinated mentioned disbelief in the efficacy of the vaccine as a reason. There is an increasing number of studies in the literature on the efficacy and safety of COVID-19 vaccines in healthy children and in those with rheumatological diseases (6,38,39). Sharing the results of these current studies with parents by health authorities and health professionals can help for overcoming the most common reasons for vaccine hesitancy reported in several studies.

Study Limitations

The main limitation of our study is its being survey-based and the data collected were patient-reported. In addition, since it is a single-center study, our results may not reflect the entire Turkish society. Therefore, further studies with larger populations are needed to confirm our results.

CONCLUSION

We report a parent-reported 75% vaccination rate in children with rheumatic disease over 12 years of age and a lower median age, lower parental age, and lower parental COVID-19 vaccination rate in unvaccinated patients. In addition, the most common reasons for not vaccinating children with rheumatic disease in this study were the fear of vaccine side effects and concerns related

to underlying rheumatic disease and medications used. These results, together with the results of previous studies, may provide clues to governments and health authorities to understand the drivers of vaccine hesitancy and help increase the coverage of vaccination programs.

Ethics Committee Approval: The study and its protocol were reviewed and approved by İstanbul University-Cerrahpaşa Cerrahpaşa, Faculty of Medicine Institutional Review Board (decision no: 179227, date: 10.09.2021).

Informed Consent: An informed consent was obtained from the patients in the questionnaire, and patients who did not want to participate were excluded from the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.Y., A.A.Y., S.Ş., K.B., Ö.K.; Design - M.Y., A.A.Y., S.Ş., K.B., Ö.K.; Data Collection and/or Processing - M.Y., F.H., A.G.; Analysis and/or Interpretation - M.Y., A.A.Y., K.B., Ö.K.; Literature Search - M.Y., F.H., A.G.; Writing - M.Y., F.H., A.A.Y.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Çalışma İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi Kurumsal İnceleme Kurulu (karar no: 179227, tarih: 10.09.2021) tarafından incelenmiş ve onaylanmıştır.

Hasta Onamı: Ankete katılan hastalardan bilgilendirilmiş onam alındı ve katılmak istemeyen hastalar çalışma dışı bırakıldı.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazar Katkıları: Konsept - M.Y., A.A.Y., S.Ş., K.B., Ö.K.; Dizayn - M.Y., A.A.Y., S.Ş., K.B., Ö.K.; Veri Toplama veya İşleme - M.Y., F.H., A.G.; Analiz veya Yorumlama - M.Y., A.A.Y., K.B., Ö.K.; Literatür Arama - M.Y., F.H., A.G.; Yazan - M.Y., F.H., A.A.Y.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

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DOI: 10.4274/jarem.galenos.2022.32932
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Evaluation of the Relationship Between Thrombolytic Treatment Complications and Laboratory Parameters in Acute Ischemic Stroke Patients

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Cite this article as: Çalık M, Öztürk D. Evaluation of the Relationship Between Thrombolytic Treatment Complications and Laboratory Parameters in Acute Ischemic Stroke Patients. J Acad Res Med 2022;12(1):36-41

ABSTRACT

Objective: We aimed to investigate the role of serum uric acid and lactate levels and mean platelet volume in predicting treatment success in patients with ischemic stroke.

Methods: One hundred and five patients who were diagnosed with cerebrovascular disease and received thrombolytic or thrombectomy treatment were included in the study. Patients were divided into two groups as patients who developed complications and who did not develop complications. Demographical characteristics, laboratory findings, the National Institutes of Health Stroke Scale (NIHSS) scores at admission and at discharge, and Modified Rankin Scale (mRS) score were investigated retrospectively.

Results: Of all patients, 58.1% of the were male. There were no differences in terms of laboratory parameters between the groups. NIHSS score at admission, NIHSS score at discharge, and mRS score were significantly higher in the group that developed complications after treatment ($p<0.05$). Laboratory values did not differ significantly between the groups. Early mortality rate in the group which developed complications was significantly higher than the group which did not develop complications ($p<0.05$). Univariate model revealed significant effectiveness of NIHSS score at admission and at discharge, and mRS score in the differentiation of patients with and without complications ($p<0.05$). In the multivariate model, a significant and independent effectiveness of the NIHSS score at discharge was observed in the differentiation of patients with and without complications (sensitivity =83.3%, positive prediction =30.8%, specificity =57.1% and negative prediction =93.8%; $p<0.05$).

Conclusion: We found no significant associations between the development of complications after thrombolytic therapy and laboratory findings. The NIHSS score may be a suitable parameter in predicting complications.

Keywords: Acute cerebral ischemia, lactate, NIHSS score, Modified Rankin Scale, uric acid

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Received Date: 24.11.2021 **Accepted Date:** 25.02.2022

J Acad Res Med 2022;12(1):36-41

INTRODUCTION

Acute cerebrovascular event (ACE) is a condition with permanent brain damage because of disruption of cerebral blood flow. Even though ACE is the second most common cause of mortality and the leading cause of disability worldwide, making decisions about the clinical course and predicting prognosis of ischemic stroke (IS) patients are still challenging (1-3).

A clinically significant relationship between serum uric acid levels and cardiovascular and cerebrovascular diseases (CVDs) has been shown (4,5). Hyperuricemia is often observed in patients with metabolic syndrome and the risk of vascular diseases is high in metabolic syndrome (6,7). Poor clinical picture after ACE has been implicated to be associated with hyperuricemia (8). There are studies showing that uric acid is a powerful antioxidant against free radicals (9,10), however, high serum uric acid levels are indicated as an independent risk factor for the development of cerebrovascular and cardiovascular disease (11). Lactate is a known by-product of anaerobic metabolism and is increased upon hypoperfusion (12). Hyperlactatemia is a biomarker of metabolic stress response and is found to be associated with mortality in critically ill patients (13,14). Several previous magnetic resonance spectroscopy and microdialysis studies have shown that lactate accumulates in ischemic brain lesions in acute stroke patients (15,16).

In our study, we aimed to investigate the role of serum uric acid and lactate levels and mean platelet volume (MPV), as well as the National Institutes of Health Stroke Scale (NIHSS) score at admission, NIHSS score at discharge, and Modified Rankin Scale (mRS) score in predicting treatment success in patients with IS.

METHODS

This retrospective study was conducted on patients who were admitted to University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Emergency Service within a 2-year period (between 01.01.2018-01.01.2020), diagnosed with CVD, and treated with only thrombolytic, only thrombectomy or thrombolytic + thrombectomy therapies in the emergency department and hospitalized in the neurology clinic of our hospital.

The blood pressure category (normal, stage I hypertension and stage II hypertension), electrocardiogram (ECG) and echocardiogram (ECHO) findings, presence of comorbidity, blood parameters [haemoglobin (HGB), MPV, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet (PLT) and red cell distribution width (RDW) values], serum uric acid and lactate levels, the NIHSS scores at admission and discharge, and mRS score were analysed in patients with regards to the presence of complications. This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles. Ethical approval was obtained from University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (decision no: 2688, date: 25.02.2020).

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency and ratio values were used. The distribution of variables was analysed with the Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data while Fisher's Exact test was used when the chi-square test conditions were not met. The effect level and cut-off value were investigated with the Receiver operating characteristic curve. The effectiveness of the NIHSS scores and mRS score in discriminating the complication status of the patients was investigated with univariate and multivariate logistic regression. The SPSS 26.0 program was used in the analysis.

RESULTS

A total of 105 patients were included in the study. Of the patients, 61 (58.1%) were male and 44 (41.9%) were female. Distribution of the comorbid diseases and demographic characteristics are indicated in Table 1.

The condition of blood pressure and ECG and ECHO findings did not differ significantly ($p>0.05$) between the groups with and without complications after thrombolytic therapy (TT). At the post-treatment period, patients who developed complications had significantly higher NIHSS score both at admission and at discharge and higher mRS score compared to the patients who did not develop any complications ($p<0.05$; Table 2). HGB, PLT, NLR, PLR, RDW, MPV, lactate, and uric acid values did not differ significantly between the groups with and without complications after treatment ($p>0.05$). The early mortality rate in the group with complications was significantly higher than the group without complications ($p<0.05$) (Table 2). Moreover, there were no significant associations between the presence of complications

Table 1. Demographic characteristics of patients

		Complication (-)	Complication (+)	p
		n (%)	n (%)	
Age	≤64	31 (29.5)	5 (20.8)	0.392$^{X^2}$
	≥65	74 (70.5)	19 (79.2)	
Gender	Female	44 (41.9)	8 (33.3)	0.440$^{X^2}$
	Male	61 (58.1)	16 (66.7)	
Comorbid chronic disease	(-)	16 (15.2)	3 (12.5)	0.733$^{X^2}$
	(+)	89 (84.8)	21 (87.5)	
Comorbid chronic disease	IHD	45 (42.9)	10 (41.7)	0.915$^{X^2}$
	HT	71 (67.6)	17 (70.8)	0.760$^{X^2}$
	DM	25 (23.8)	8 (33.3)	0.335$^{X^2}$
	CVE	19 (18.1)	5 (20.8)	0.756$^{X^2}$
	Other	18 (17.1)	4 (16.7)	0.955$^{X^2}$

CVE: cerebrovascular event, DM: diabetes mellitus, HT: hypertension, IHD: ischemic heart disease, $^{X^2}$Spearman Rho test

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and the duration of the treatment (p>0.05; Table 2a and Table 2b).

In the analysis with univariate model, significant efficiencies of NIHSS score at admission, NIHSS score at discharge, and mRS score was observed in distinguishing patients with and without complications. In the analysis with reduced multivariate model, a significant and independent efficiency of the NIHSS score at discharge was observed in discriminating patients with and without complications (odds ratio: 1.17, 95% confidence interval: 1.07-1.28, p=0.001) (Table 3).

A significant efficacy of the NIHSS score at discharge was observed in the discrimination of patients who developed and did not develop complications after treatment [Area under the curve (AUC) =0.766 (0.661-0.872)]. A significant efficacy of the cut-off value of 10 in the NIHSS score at discharge was observed in the differentiation of patients with and without complications [AUC =0.702 (0.595-0.810)]. Sensitivity, positive prediction, specificity, and negative prediction were found as 83.3%, 30.8%, 57.1%, and 93.8%, respectively (Figure 1).

DISCUSSION

In the literature, a debate about the role of hemogram parameters on the pathogenesis of stroke is still going on. In this study, we

Table 2a. Evaluation of the post-treatment status of the patients

	Complication (-)		Complication (+)		p
	Min-max	Median	Min-max	Median	
NIHSS score at admission	4.0-22.0	10.0	4.0-42.0	16.0	0.001[m]
NIHSS score at discharge	0.0-22.0	8.0	3.0-35.0	16.5	0.001[m]
mRS score	0.0-6.0	4.0	0.0-6.0	5.0	0.008[m]
HGB	75.0-169.0	131.0	77.0-189.0	138.5	0.331[t]
PLT	97.0-592.0	219.0	101.0-609.0	221.5	0.945[m]
NLR	0.4-15.4	2.4	0.4-15.5	2.4	0.751[m]
PLR	14.5-397.3	101.8	13.8-388.6	101.5	0.444[m]
RDW	64.0-218.0	139.0	63.0-221.0	139.0	0.981[m]
MPV	7.3-12.2	9.5	7.0-13.0	9.6	0.699[t]
Lactate	0.8-7.0	1.7	1.1-7.7	1.9	0.421[m]
Uric acid	1.8-11.5	5.3	2.6-13.3	8.2	0.897[t]

HGB: haemoglobin, MPV: mean platelet volume, NIHSS: The National Institutes of Health Stroke Scale, mRS: The Modified Rankin Scale, NLR: heutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, PLT: platelet, RDW: red cell distribution width, [m] Mann-Whitney U test/[t]t-test

Table 2b. Evaluation of the post-treatment status of the patients

		Complication (-)	Complication (+)	p
		Mean ± SD/n (%)	Mean ± SD/n (%)	
Blood pressure	Normal	28 (26.7)	4 (16.7)	0.438[X²]
	Stage I hypertension	24 (22.9)	8 (33.3)	
	Stage II hypertension	53 (50.5)	12 (50.0)	
ECG	NSR	74 (70.5)	15 (62.5)	0.446[X²]
	AF	31 (29.5)	9 (37.5)	
ECHO findings				
Normal ECHO		68 (64.8)	18 (75.0)	0.471[X²]
Enlarged right atrium and ventricle		7 (6.7)	2 (8.3)	
Enlarged left atrium and ventricle		19 (18.1)	3 (12.5)	
Segmentary wall motion abnormality		11 (10.5)	1 (4.2)	
One-month mortality	(+)	21 (20.0)	10 (41.7)	0.025[X²]
	(-)	84 (80.0)	14 (58.3)	
Duration of treatment (min)	0-59	13 (12.4)	2 (83)	0.085[X²]
	120	51 (48.6)	9 (37.5)	
	180	26 (24.8)	12 (50.0)	
	240	15 (14.3)	1 (4.2)	

AF: atrial fibrillation, ECG: electrocardiogram, ECHO: echocardiogram, NSR: normal sinus rhythm, [X²]Spearman Rho test

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Table 3. Logistic regression analysis

	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
NIHSS score at admission	1.164	1.059-1.279	0.002	-	-	-
NIHSS score at discharge	1.179	1.079-1.288	0.001	1.179	1.079 - 1.288	0.001
mRS score	1.532	1.088-2.156	0.014	-	-	-

NIHSS: The National Institutes of Health Stroke Scale, OR: odds ratio, CI: confidence interval

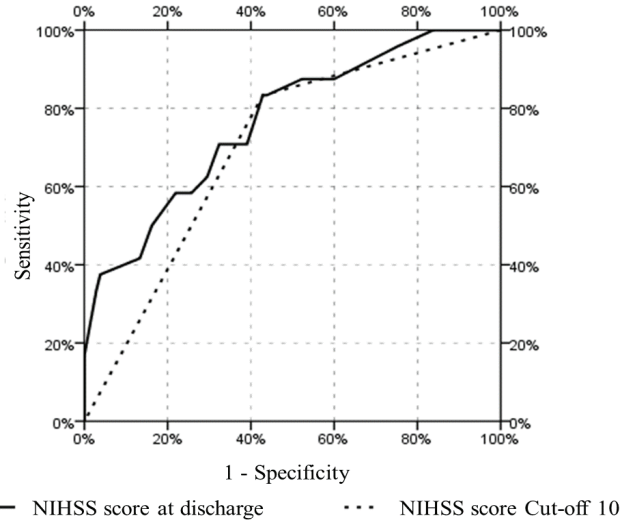

Figure 1. Sensitivity and specificity of NIHSS in predicting complication
NIHSS: The National Institutes of Health Stroke Scale

investigated the relationship between serum uric acid, lactate and MPV values and treatment success in patients with IS. Moreover, common scales which measured the disability of the patient after stroke and severity of the stroke, including NIHSS and mRS were analysed with regards to the presence of the complications after treatment.

Previously, it was reported that the hematologic parameters were significantly altered in patients with IS (17). Yigit et al. (18) indicated that anaemia was a risk factor for recurrence of IS in patients with malignancy. Another study reported that MPV was associated with the severity of acute IS (19). On the other hand, increased NLR at the admission was reported to be an independent factor related to poor prognosis and poor 90-day outcome in patients with intracerebral haemorrhage (ICH) and it was suggested to be a prognostic marker in spontaneous ICH patients (20). In our study, no significant differences in terms of haematological parameters evaluated between the patients with and without complications after TT were found.

Lactate is produced as the result of anaerobic glycolysis. When the glucose is deprived in the brain, lactate is used as an alternative energy source for the metabolic activities in the brain (21). Previously, elevated blood lactate levels in stroke patients at admission were suggested to indicate higher risk of 1-, 3-, and 12-month mortality (22), Another study, it was shown that lactate level in cerebrospinal fluid (CSF), but not in blood, was found to be significantly higher in patients with acute stroke and it was suggested that CSF lactate level might be used as a marker for the evaluation of stroke severity (23). We also found no significant differences between the patients with and without complications with regards to serum lactate levels.

Hyperuricemia and accompanying dyslipidaemia in patients with acute stroke have been implicated to be risk factors for acute IS (24,25). Post-ischemic hyperuricemia in diabetic patients was reported to be associated with mortality and recurrent vascular events in IS patients (26). Moreover, Karagiannis et al. (27) reported a significant association between increased serum uric acid levels and early mortality. However, we did not find any significant differences in terms of uric acid levels between the patients who developed complications and the patients who did not develop complications.

Early recanalization positively affects the prognosis in patients with acute IS (28) by reducing the mortality and disability in the patients (29). Although, the risk of development of complications after intravenous recombinant tissue plasminogen activator treatment was reported to increase with older, presence of severe neurological deficit, hypertension, diabetes mellitus, and early signs of infarction in computed tomography, there were contradictory results regarding those (30-33). High NIHSS score before the TT has been implicated to be a risk factor for haemorrhagic transformation after TT (34,35). Moreover, NIHSS score higher than 25 is a contraindication for TT (33). The most common and serious complication of TT is haemorrhagic transformation and poor clinical prognosis is encountered in case of intracranial haemorrhage (36,37). The mRS is used to measure the disability of the patient after IS and is indicated to be an important tool for prediction outcomes after discharge (38-40). In our study, patients who developed complications after TT had higher NIHSS scores both at admission and at discharge, as well as higher mRS scores. Moreover, in the univariate model, significant efficacies of NIHSS scores both at admission and at discharge, as well as mRS scores were detected. On the other hand, NIHSS score at discharge was found to be a sensitive and specific predictor of development of complication in IS patients.

Study Limitations

This study had some limitations. First, the sample size was small, therefore, a larger group of patients could be included. Secondly, we did not measure the lactate levels in CSF or did not perform magnetic resonance spectroscopy analysis for the patients.

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CONCLUSION

Predicting the development of complications after TT in patients with acute IS is crucial to prevent the complications and mortality. In the present study, NIHSS score was found to be a significant determinant in predicting complications in patients with IS. Therefore, NIHSS score may be suggested to be useful for the prediction of the development of the complications in the patients with IS. Future studies with larger populations and more detailed examinations are required to investigate the relationship between the parameters and complications and to predict the prognosis.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles. Ethical approval was obtained from University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (decision no: 2688, date: 25.02.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - D.Ö.; Concept - D.Ö.; Design - M.Ç.; Data Collection and/or Processing - D.Ö.; Analysis and/or Interpretation - M.Ç.; Literature Search - D.Ö., M.Ç.; Writing - M.Ç.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma Helsinki Bildirgesi Etik İlkelere uygun olarak yapılmıştır. Etik onay Sağlık Bilimleri Üniversitesi, Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan (karar no: 2688, tarih: 25.02.2020) alınmıştır.

Hasta Onamı: Retrospektif çalışma.

Hakem Değerlendirmesi: Editörler kurulu ve editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazar Katkıları: Cerrahi ve Medikal Uygulama - D.Ö.; Konsept - D.Ö.; Dizayn - M.Ç.; Veri Toplama veya İşleme - D.Ö.; Analiz veya Yorumlama - M.Ç.; Literatür Arama - D.Ö., M.Ç.; Yazan - M.Ç.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

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