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Inflammatory Biomarkers and Echocardiographic Findings in Acute Rheumatic Fever Patients

Akut Romatizmal Ateş Hastalarında Yeni Biyomarkerler ve Ekokardiyografik Bulgular

Naile Gasımova[1], Ahmet Sert[2]

[1]Selcuk University School of Medicine, Department of Pediatrics, Konya, Turkey
[2]Selcuk University School of Medicine, Department of Pediatric Cardiology, Konya, Turkey

Abstract

Aim: Acute rheumatic fever (ARF) is an inflammatory disease that develops after Group A Streptococcal (GAS) tonsillopharyngitis in genetically susceptible individuals. We aimed to examine the clinical, laboratory, and echocardiographic findings of the patients diagnosed and followed up with ARF.

Material and Method: 55 patients under the age of 18 who were hospitalized and followed up with the diagnosis of ARF between January 2017 and January 2019 were included in this retrospective study. All cases were diagnosed with ARF according to the 2015 revised Jones criteria according to the intermediate-risk group. Gender, age, time of admission, physical examination findings, laboratory findings, echocardiographic findings, and data meeting major and minor diagnostic criteria of all patients diagnosed with ARF were recorded. Echocardiography and electrocardiography were performed on all patients. Inflammatory biomarkers were calculated using laboratory parameters. The data before the treatment and at the 8th week of the treatment were compared.

Results: 31 (56.4%) of the patients were female and 24 (43.6%) were male, the mean age was 13.70±2.44 years (7-18 years). The highest number of patients was in the 9-14 age group. The most frequent hospital admission season was winter. Arthritis and carditis were the most common major criteria. Post-treatment body weight, height, body mass index, and systolic and diastolic blood pressure values of the patients were statistically significantly higher than before treatment ($p<0.001$). The white blood cells (WBC), neutrophil (NE), monocyte (MO), eosinophil (EO), platelets (PLT), mean platelet volume (MPV), mean corpuscular hemoglobin concentration (MCHC), plateletcrit (PCT), C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Neutrophil-to-lymphocyte ratio (NLR), Neutrophil-to-monocyte ratio (NMO), and Systemic Inflammatory Index (SII) values decreased significantly after treatment. Before treatment, a moderate positive correlation was found between MPV and TLO (p: 0.045, r: -0.2712), MPV and LMO (p: 0.041, r: -0.2762), and a positive correlation at a moderate level between MPV and MPV/L (p: 0.001, r: 0.431). On the other hand, a high positive correlation was observed between SII and WBC (p: 0.001, r: 0.652), SII and NE (p: 0.001, r: 0.759), and SII and NLO (p: 0.001, r: 0.882) before treatment, while a moderate positive correlation was found between SII and TLO (p: 0.001, r: 0.598). Aortic valve regurgitation was significantly reduced with treatment. There was no significant difference in LVM and LVMI values after treatment (p:0.143, p: 0.672, respectively).

Conclusion: Our results suggests that there is no adverse effect on LV remodeling after treatment in patients with ARF. We believe that inflammation can be followed easily by using inflammatory parameters in the acute and post-treatment periods of the disease.

Keywords: Acute rheumatic fever, childhood, echocardiography, inflammation, rheumatic heart disease

Öz

Amaç: Akut romatizmal ateş (ARA) Grup A Streptokok (GAS) tonsillofarenjiti geçiren genetik olarak duyarlı bireylerde, enfeksiyonu takiben gelişen inflamatuvar bir hastalıktır. Bu çalışmada ARA tanısı ile takip edilen hastaların klinik, laboratuar ve ekokardiyografik bulgularının incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya Ocak 2017-Ocak 2019 tarihleri arasında 18 yaş altı ARA tanısı ile yatırılarak takip edilen 55 hasta dahil edildi. Tüm olgularda ARA tanısı 2015 yılı revize Jones kriterleri ile orta-risk grubuna göre konuldu. ARA tanısı konan tüm hastaların; cinsiyeti, yaşı, başvuru zamanı, fizik muayene bulguları, laboratuar bulguları, ekokardiyografi bulguları, major ve minör tanı kriterleri sağlayan verileri kaydedildi. Tüm hastalara ekokardiyografi ve elektrokardiyografi yapıldı. Laboratuvar parametreleri kullanarak inflamatuar biyobelirteçler hesaplandı. Tedavi öncesi ve tedavinin 8. haftasındaki veriler kıyaslandı.

Bulgular: Hastaların 31'i (%56,4) kız ve 24'ü (%43,6) erkek, yaş ortalaması 13,70±2,44 yıl (7-18 yıl) idi. En fazla hasta 9-14 yaş arasında görüldü. En sık hastaneye başvuru mevsimi kış idi. Major kriterlerden en sık kardit ve artrit görüldü. Hastaların tedavi sonrası vücut ağırlığı, vücut kitle indeksi, sistolik ve diyastolik kan basıncı değerleri tedavi öncesine göre istatistiksel olarak anlamlı yüksek bulundu ($p<0,001$). Beyaz kan hücreleri (WBC), nötrofil (NE), monosit (MO), eozinofil (EO), trombosit (PLT), ortalama trombosit hacmi (MPV), ortalama korpusküler hemoglobin konsantrasyonu (MCHC), trombositkrit (PCT), C-reaktif protein (CRP), Eritrosit Sedimentasyon Hızı (ESR), Nötrofil-lenfosit oranı (NLR), Nötrofil-monosit oranı (NMO) ve Sistemik İnflamatuar İndeks (SII) değerleri tedaviden sonra önemli ölçüde azalmış bulundu. MCH, RDW, PDW, L/CRP değerleri tedavi sonrasında anlamlı olarak artmıştı. Hastaların tedavi öncesi MPV ile TLO (p: 0,045, r: -0,2712), MPV ile LMO (p: 0,041, r: -0,2762), MPV ile MPV/L arasında pozitif yönde orta (p: 0,001, r: 0,431) düzeyde korelasyon saptanırken; tedavi öncesi SII ile WBC (p: 0,001, r: 0,652), SII ile NE (p: 0,001, r: 0,759) ve SII ile NLO arasında pozitif yönde yüksek (p: 0,001, r: 0,882) korelasyon, SII ile TLO arasında ise pozitif yönde orta (p: 0,001, r: 0,598) düzeyde korelasyon olduğu tespit edilmiştir. Tedavi ile aort kapak yetmezliğinin anlamlı olarak azalmış olduğu gösterildi. Tedavi sonrasında LVM ve LVMI değerlerinde ise anlamlı fark tespit edilmedi (sırasıyla p:0,143, p: 0,672).

Sonuç: Çalışmamızdaki hastaların klinik bulgularının sıklığı literatürle benzerdir. ARA'lı hastalarda tedavi sonrası LV remodeling üzerinde olumsuz etki olmadığını düşündürmektedir. Hastalığın akut ve tedavi sonrası sürecinde inflamatuar parametreler kullanılarak inflamasyon takibinin kolaylıkla yapılabileceğini düşünmekteyiz.

Anahtar Kelimeler: Akut romatizmal ateş, çocukluk çağı, ekokardiyografi, romatizmal kalp hastalığı

Corresponding *(İletişim)*: Naıla GASIMOVA, Selcuk University School of Medicine Department of Pediatrics, Konya, Turkey
E-mail *(E-posta)*: uzm_dr.naile_gasimova@yahoo.com
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INTRODUCTION

Acute rheumatic fever (ARF) is an inflammatory disease that affects the joints, heart, brain and skin, resulting from an abnormal immune response to Group A Streptococcal (GAS) infection.[1] In genetically susceptible individuals, after an average of three weeks latent period from GAS tonsilopharyngitis, a nonsuppurative, multisystemic, inflammatory connective tissue disease that causes rheumatic heart disease occurs as a result of widespread systemic involvement in the heart, joints, and brain, and damage to the collagen fibers and heart valves of the connective tissue.[1] While the incidence and importance of acute rheumatic fever (ARF), which is still an important public health problem, is decreasing in developed countries, its importance continues in developing countries.[2] In developed countries, the incidence of the disease has decreased in recent years thanks to the gradual improvement of living conditions, early detection of the disease, timely and appropriate start of antibiotic treatment and prophylaxis, public awareness, close follow-up of patients, and the use of non-invasive diagnostic methods such as echocardiography (ECHO).[3]

ARF is one of the leading causes of acquired heart disease in the pediatric age group worldwide.[3] ARF is more common in children aged 5-15 years.[4] Globally, it is estimated that approximately 500,000 new cases of ARF are diagnosed annually and approximately 230,000 people die from the disease each year. ARF is among the leading causes of cardiovascular death in the first 50 years of life.[5]

The diagnosis of ARF is made using the updated Jones criteria consisting of clinical and laboratory findings, as reported by the American Heart Association (AHA) in 2015.[6] Since the frequency of the disease shows a heterogeneous course in the world and the risk situation changes accordingly, it is thought that a single diagnostic criterion will not be sufficient when diagnosing in all societies, diagnostic criteria have been arranged according to two different groups as risky in order to prevent misdiagnosis in regions where the disease is rare and not to miss a diagnosis in regions where the incidence of the disease is high.[6] The incidence of ARF varies in Turkey, in regions and even in different provinces of the same regions. According to a recent study, the estimated incidence rate of ARF was reported as 8.84/100 000 in Turkey.[7]

We aimed to examine the clinical, echocardiographic and laboratory findings of the patients diagnosed with ARF and followed up in this study.

MATERIAL AND METHOD

This retrospective study was conducted in patients hospitalized with the diagnosis of ARF between January 2017 and January 2019. Necessary permissions were obtained for the protocol of the study, and the Selcuk University Local Ethic Committee was approved the study (approval number: 2019/321, approval date: 13.11.2019).

A total of 55 patients under the age of 18 who were hospitalized and followed up with the diagnosis of ARF were included in the study. The clinical, laboratory and echocardiographic findings of the patients were compared before and after the treatment. We also examined the relationship between new inflammatory markers and acute phase reactants and hematological parameters. In all cases, the diagnosis of ARF was made according to the 2015 revised Jones criteria according to the medium-high risk group 6.

Gender, age, time of admission, physical examination findings, laboratory findings, echocardiographic findings, and major and minor criteria of all patients diagnosed with ARF were recorded. The patient's fever, arthritis (monoarthritis, polyarthritis), cardiovascular system examination (tachycardia, murmur), ECG findings, erythema marginatum, subcutaneous nodule, Sydenham chorea were also recorded from the patient file records. BMI was calculated with the formula weight (kg)/height (m^2). After resting for 5 minutes, systolic and diastolic blood pressures were measured with a cuff suitable for the patient's arm at heart level. ECG findings were interpreted by a same, single pediatric cardiologist.

ECHO examination was performed with the Philips EPIQ 7C (USA) device, by taking multiple orthogonal parasternal, apical and subcostal images of the patients lying in the left lateral decubitus position by the same pediatric cardiologist. Traditional ECHO evaluation includes measurements of LV end-diastolic and end-systolic diameter, septal and LV posterior wall thicknesses in diastole and systole, LV ejection fraction (EF) and LV fractional shortening (FS) from the parasternal long-axis view. EF and FS were calculated using Teichholz's M-mod formula. Left ventricular mass calculated by the formula developed by Devereux et al.[8]:

$$\mathbf{LVM=0.8\{1.04[LVIDD+İVS(d)+LVPWD(d))^3-(LVIDD)^3]\}+0.6}$$

The left ventricular mass index was calculated by dividing the LVM length by the 2.7 strength (m2.7).

Laboratory Parameters

Autoanalyzer was used on Beckman Coulter DXH 800 and Beckman Immage 800 devices. Inflammation parameters were neutrophil lymphocyte ratio (NLR) which calculated as peripheral blood neutrophil count divided by total lymphocyte count, platelet lymphocyte ratio (PLR) which calculated as platelet count divided by lymphocyte count, lymphocyte monocyte ratio (LMR) which calculated as lymphocyte count divided by monocyte count, neutrophil monocyte ratio (NMO) which calculated as neutrophil count divided by monocyte count, lymphocyte CRP ratio (L/CRP) which calculated as lymphocyte count divided by CRP value, MPV lymphocyte ratio (MPV/L) which calculated as MPV value divided by lymphocyte count, and Systemic Inflammatory Index (SII) which calculated as dividing the platelet count x neutrophil count/lymphocyte count.

The data before the treatment and at the 8th week of the treatment were compared. Aspirin 75-80 mg/kg/day in 4

doses was given to 4 patients diagnosed with isolated arthritis and mild carditis, naproxen was given in 2 doses of 15 mg/kg/day to 2 patients with isolated arthritis, and prednisolone 2mg/kg/day was given in divided doses to 49 patients with moderate and severe carditis. Absolute bed rest was started. Serial ECO was performed at regular intervals. All patients were given secondary prophylaxis and patients with valve findings were given infective endocarditis prophylaxis.

Statistical Analysis

All data obtained from patient files, examination findings and laboratory parameters, and cardiological evaluation findings were recorded in the dataset. These recorded data were analyzed with the Statistical Analysis for Social Sciences (SPSS) package program version 23.0. Conformity to normal distribution was evaluated with the Shapiro Wilk test. Normally distributed data were presented as mean ± standard deviation. Data that did not show normal distribution were shown as median (minimum-maximum). Categorical data were presented as frequency % (percent). Chi-square test was used to compare categorical data. The relationship between continuous variables was examined by correlation analysis. In the comparisons before and after the treatment, the data suitable for normal distribution were analyzed with the paired-t test, and the data not suitable for the normal distribution were analyzed with the Wilcoxon test. The McNemar test was used to compare bi-state categorical variables before and after treatment. Values of categorical data were presented with bar and pie charts. For statistical significance level, $p<0.05$ was accepted. All analyzes were performed by an experienced statistician.

RESULTS

A total of 55 patients included in the study, 31 (56.4%) were female and 24 (43.6%) were male, and the female/male ratio was 1.29. The mean age of patients with ARF was 13.70±2.44 years. The median age of the patients was 13.50 years, while the youngest patient was 7 years old, and the oldest patient was 18 years old. There was no statistically significant difference in terms of mean age according to gender ($p>0.05$). The most ARF patients were between the ages of 9-14. No patients under the age of five were identified. Considering the season of admission of the patients to the hospital, it was most common in winter with 30 (54.5%) patients. The season of admission to the hospital was most common in winter with 30 patients (54.5%).

Body weight, body mass index, systolic and diastolic blood pressure values of the patients included in the study were statistically significantly higher after treatment compared to before treatment ($p <0.001$).

The most common ARF major criteria in our patients were carditis (89%) and arthritis (76.3%). Considering the rates of single and coexistence of the major criteria, isolated arthritis in 4 patients (7.2%), isolated carditis in 6 patients (11%), carditis and chorea in 7 patients (12.7%), arthritis and carditis in 30 patients (54%, 5), arthritis, carditis and erythema marginatum in 2 patients (3.6%), arthritis, carditis and subcutaneous nodule in 1 patient (1.8%), polyarthralgia in 2 patients (without arthritis), polyarthralgia in 3 patients (3.6%) and coexistence of polyarthralgia and carditis were reported in 3 patients (3.6%). Polyarthritis was determined in 24 (57%) of 42 patients with major joint findings, monoarthritis in 13 (31%) and polyarthralgia (without arthritis) in 5 (12%) patients (**Table 1**).

Table 1. Distribution of major findings of patients in the medium-high risk group according to "2015 revised Jones criteria"

Major Criteria	All Patients (n: 55)	
	Number (n)	Frequency (%)
Arthritis/Polyarthralgia	42	76.3
Carditis	49	89
Rheumatic Chorea	7	12.73
Erythema Marginatum	2	3.6
Subcutaneous Nodule	1	1.82

When the patients diagnosed with ARF were examined according to minor criteria, 54 (98.18%) of the patients had elevated ESR, 45 (81.81%) of patients had elevated CRP, 15 (27.27%) patients had monoarthralgia, 4 (7%, 27) patients had PR prolongation, and fever were determined in 2 (3.6%) patients (**Table 2**).

Table 2. Distribution of minor findings of patients in the moderate-high risk group according to "2015 revised Jones criteria"

Minor criteria	All Patients (n: 55)	
	Number (n)	Frequency (%)
Monoarthralgia	15	27.27
Elevated CRP	45	81.81
Elevated ESR	54	98.18
Prolonged PR	4	7.27
Fever	2	3.6

Abbreviations: CRP: C-reactive Protein, ESR: Erythrocyte Sedimentation Rate, PR: P-R distance in electrocardiography

Considering the positivity rates of CRP elevation, ESR elevation, and PR prolongation before and after treatment, which are minor criteria, CRP elevation was present in 81.8% of patients before treatment, while this rate decreased to 16.3% after treatment. Similarly, the rate of elevated ESR decreased from 98.1% to 16.4%. While PR prolongation was detected in 7.3% of patients before treatment, this rate decreased to 0% after treatment, that is, PR prolongation was not observed in any patient (**Table 3**).

Table 3. Distribution of minor criteria before and after treatment

Minor criteria		Number (n)	Frequency (%)
Elevated CRP	Pre-treatment	45	81.8
	Post-treatment	9	16.3
Elevated ESR	Pre-treatment	54	98.1
	Post-treatment	9	16.4
Prolonged PR	Pre-treatment	4	7.3
	Post-treatment	0	0

Abbreviations: CRP: C-reactive Protein, ESR: Erythrocyte Sedimentation Rate, PR: P-R distance in electrocardiography

When the patients diagnosed with ARF were examined according to the supportive findings, ASO elevation was detected in 48 (87.27%) and AGBHS was found to be grown in 2 (6%) of 33 patients who had a throat culture. Aortic valve insufficiency was detected in 41 patients before treatment in ARF patients while it was detected in 26 patients after treatment. Post-treatment recovery rate of patients with aortic valve insufficiency was 36.6%. There was a statistically significant difference between before and after treatment in terms of the presence of aortic valve insufficiency (p:<0.001). Mitral valve insufficiency was present in 49 patients before treatment in ARF patients while it was detected in 46 patients after treatment. There was no statistically significant difference between pre- and post-treatment in terms of the presence of mitral valve insufficiency (p: 0.250)

In our study, when the laboratory values of the patients were examined according to the treatment, a statistically significant difference was found in the hemogram parameters of WBC, PLT, MCV, MCH, MPV, NE, MO, RDW, PDW, PCT, MCHC, EO compared before and after treatment. WBC, PLT, MPV, NE, PCT, MCHC, MO values decreased significantly after treatment, while MCH, RDW, PDW values increased significantly after treatment (**Table 4**).

In our study, when the laboratory values of the patients were examined according to the treatment, a statistically significant difference was found when the CRP, ESR, NLR, TLR, NMO, L/CRP, SII were compared before and after the treatment. CRP, ESH, NLR, NMO, TLR, EO, and SII values decreased significantly after treatment, whereas L/CRP values increased significantly after treatment (**Table 5**).

When the echocardiographic examination results before and after treatment in ARF patients were compared, a decrease in LVIDd and an increase in EF were statistically significant after treatment. No significant difference was found in the evaluation of LVM and LVMI (**Table 6**).

Table 4. Hemogram values of ARF patients before and after treatment

	Pre-Treatment		Post-Treatment		P values
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
WBC (10^3/µl)	15.63±6.22	14.2 (6.5 - 34.5)	10.82±3.13	10.2 (6.3 - 20.7)	<0.001
HGB (g/dL)	13.2±1.41	13.4 (9.9 - 15.8)	13.51±0.93	13.5 (11.7 - 15.3)	0.129
HCT (%)	40.14±4.5	40.2 (30 - 49.1)	40.63±2.82	40.6 (34.2 - 46.5)	0.445
PLT (10^3/µl)	428.11±118.98	415 (220 - 779)	305.11±111.06	271 (160 - 612)	<0.001
MCV (fL)	80.33±5.1	80.1 (70 - 100)	81.45±5.03	81.3 (68.7 - 98.8)	<0.001
MCH (pg)	26.37±1.82	26.3 (22.8 - 34)	27.19±2.00	27.4 (23.2 – 33.6)	<0.001
MPV (fL)	7.68±0.93	7.7 (6.1 - 10.7)	7.44±0.86	7.5 (6 - 9.7)	0.005
NE (10^3/µl)	11.83±5.75	10.6 (3.7 - 28)	6.87±2.89	6.8 (2 - 15)	<0.001
LY (10^3/µl)	2.71±0.84	2.6 (1.14 - 4.9)	2.79±0.91	2.7 (1.2 - 6.2)	0.670
RDW (%)	14.92±2	14.4 (12.3 - 24)	17.69±2.61	17.4 (12.9 - 24.4)	<0.001
PDW (fL)	16.36±0.61	16.3 (15.4 - 18.6)	16.63±0.66	16.6 (13.9 - 17.9)	<0.001
PCT (%)	0.31±0.09	0.3 (0.16 - 0.61)	0.22±0.08	0.19 (0.12 - 0.46)	<0.001
MCHC (g/dL)	32.76±1.09	32.8 (26.6 - 34.2)	27.19±2.01	27.4 (23.2 - 33.6)	<0.001
EO (10^3/µl)	0.11±0.35	0.02 (0 - 2.31)	0.13±0.31	0.05 (0 - 2.1)	<0.001
BA (10^3/µl)	0.05±0.06	0.03 (0 - 0.34)	0.05±0.12	0.03 (0 - 0.8)	0.355
MO (10^3/µl)	1.01±0.5	0.93 (0.17 - 2.26)	0.84±0.33	0.78 (0.4 - 1.9)	<0.001

Abbreviations: WBC: white blood cell count, Hgb: Hemoglobin, HCT: hematocrit, PLT: Platelet count, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MPV: Mean platelet volume, NE: Neutrophil, LY: Lymphocyte, RDW: Erythrocytes distribution width, PDW: Platelet distribution width, PCT: Mean platelet percentage, MCHC: Mean cell hemoglobin concentration, EO: Eosinophil, BA: Basophil, MO: Monocyte

Table 5. Comparison of inflammation parameters before and after treatment in ARF patients

	Pre-Treatment		Post-Treatment		P values
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
CRP (mg/L)	53.52±63.21	18 (0.4 - 235)	4.52±5.71	2.21 (0.1 - 27)	<0.001
ESR (mm/hour)	59.73±22.46	57 (13-119)	11.95±8.21	11 (2 - 33)	<0.001
N/L ratio	4.57±2.42	4.23 (0.87-11.25)	2.76±1.62	2.21 (0.52 - 8.07)	<0.001
Plt/L ratio	169.75±82.35	158 (16 - 501)	122.47±60.72	103 (35.3 - 344)	<0.001
L/M ratio	3.45±1.97	2.8 (1.2 - 9.75)	3.62±1.32	3.7 (1 - 7.75)	0.149
N/M ratio	13.74±9.58	11.96 (2.91 - 65.29)	8.83±4.15	8.36 (2.86 - 28.25)	<0.001
L/CRP ratio	0.63±1.28	0.14 (0.01 - 6.5)	4.14±9.85	1.04 (0.12 - 62)	<0.001
MPV/L ratio	3.16±1.2	2.96 (1.61 - 6.62)	2.96±1.1	2.72 (1.23 - 8.08)	0.346
SII	2050.16±1566.63	1713.8 (361.05- 8763.75)	837.68±581	566.5 (195.8- 2827.2)	<0.001

Abbreviations: CRP: C-reactive protein, ESH: Sedimentation, N/L: Neutrophil Lymphocyte ratio, T/L: Platelet Lymphocyte ratio, L/M: Lymphocyte Monocyte ratio, N/M: Neutrophil Monocyte ratio, L/CRP: Lymphocyte CRP, MPV/L: Mean Platelet volume Lymphocyte ratio, SII: Systemic Inflammatory Index

Table 6. Comparison of echocardiographic parameters of ARF patients before and after treatment

	Pre-Treatment		Post-Treatment		P values
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
İVSd (mm)	7.54±1.31	7.7 (4 - 10)	7.87±1.11	8 (5 - 11)	0.119
LVIDd (mm)	38.54±7.77	39 (5.5 - 50.2)	38.01±5.14	38.4 (23.5 - 47.6)	0.008
LVPWd (mm)	8.12±4.11	7.6 (5 - 36.5)	7.91±2.31	7.7 (5 - 21)	0.459
İVSs (mm)	9.07±2.1	8.8 (6.1 - 21)	8.85±1.18	9 (6.1 - 11)	0.508
LVIDs (mm)	23.67±4.25	23.6 (9.6 - 40)	22.94±5.46	22.9 (8.3 - 39.6)	0.238
LVPWs (mm)	9.73±2.31	9.6 (6 - 21.8)	9.5±2.26	9.2 (6.1 - 22)	0.439
EF (%)	70.6±4.47	71 (63 - 79)	72.28±4.16	72 (65 - 80)	0.040
FS (%)	39.8±3.91	40 (34 - 49)	40.72±4	40 (33 - 53)	0.223
LVM (g)	93.34±36.78	85.07 (0.6-193.42)	101.25±47.93	91.66 (8.17-346.95)	0.143
LVMI (g/m2,7)	37.87±16.63	36.43 (0.19 - 86.02)	35.92±14.92	34.53 (2.59 – 101)	0.672

Abbreviations: IVSd: Interventricular septum in diastole, LVPWd: Left ventricular posterior wall thickness in diastole, LVIDd: Left ventricular end-diastolic diameter, IVSs: Interventricular septum in systole LVIDs: Left ventricular end-systolic diameter, LVPWs: Systole left ventricular posterior wall thickness EF: Ejection fraction, FS: Fractional shortening, LVM: Left ventricular mass, LVMI: Left ventricular mass index

The correlation between pre- and post-treatment hemogram and inflammation parameter values and MPV was investigated. Accordingly, it was determined that there was a weak negative correlation between MPV before treatment and TLR, LMO, and CRP after treatment, a moderate positive correlation between MPV/L, a positive high correlation between pretreatment SII and WBC, NLR, NE, and a moderate positive correlation between TLR. No correlation was found between SII and pre- and post-treatment ESR, and CRP.

DISCUSSION

In this retrospective study, clinical, laboratory and echocardiographic features of patients hospitalized with the diagnosis of ARF before and after treatment were examined. Inflammatory parameters were also studied.

The mean age of ARF patients in our study was 13.70±2.44 years. The oldest of the patients was 18 years old and the youngest was 7 years old. When the cases were classified according to age groups, the most patients were between the ages of 9-14 and constituted 58.1% of all cases. We did not have any patients under the age of five, 1 (1.9%) between the ages of 5 and 8, and 22 (40%) patients over the age of 15 were identified. In the study of Ozer et al., which included 129 children with ARF in 1999-2000, the mean age of the patients was 11.2 ± 2.73 years, Boyarchuk et al. found 10.5 ± 1.85 years, and Gurses et al. determined the mean age as 11±2.8 years. [9-11] In a study conducted in Israel between 2000 and 2005, it was reported that 79.5% of the patients were in the 5-14 age group, 16% were over the age of 15, and 4.5% were between the ages of 25-29.[12] In a retrospective study of 1103 patients in Turkey in 2021, the mean age of ARF patients was reported as 11 ± 2.7 years. Studies conducted in India, Australia and Aborigines show similarities with the literature.[13,14] In this context, the mean age of the patients we examined in our study is consistent with the literature.

The incidence of ARF is equal in boys and girls.[15] In the study of Gungor et al. in 2014, 46.5% of the patients were female and 53.5% were male.[16] In a multicenter study conducted in 2021, the male/female ratio was reported as 1.09 . In our study, 31 (56.3%) of the patients diagnosed with ARF were female and 24 (43.6%) were male. The female to male ratio was 1.29. In our study, the rate of female gender was higher in patients diagnosed with ARF, but the difference was not statistically significant.

Since throat infections due to GAS are most common in spring and winter, ARF is most common in these seasons.[17] In our study, 30 (54.5%) of the patients were applied in winter, 13 (23.6%) were applied in summer, 11 (20%) were applied in spring, and 1 (1.8%) were applied in autumn, according to the order of admission season. This result suggests that GAS infection may cause ARF not only in winter but also in other seasons in susceptible individuals.

In our study, when the major criteria during the acute attack of 55 patients with ARF were examined, isolated arthritis in 4 patients (7.2%), isolated carditis in 6 patients (11%), carditis and chorea in 7 patients (12.7%), arthritis and carditis in 30 patient (54.5%), arthritis, carditis and erythema marginatum in 2 patients (3.6%), arthritis, carditis and subcutaneous nodule in 1 patient (1.8%), polyarthralgia in 2 patients (without arthritis) (% Polyarthralgia and carditis were found together in 3, 6 and 3 patients (5,4%). Considering the rates of major criteria in ARF, carditis was reported 30-70%, arthritis 40-70%, chorea 10-30%, erythema marginatum below 5%, and subcutaneous nodule 0-10%.[17] In the study by Carapetis et al. and in Australia, carditis was 55%, arthritis 55%, chorea 28%, erythema marginatum 0.5% and subcutaneous nodule 0.5%, in a study conducted in Ukraine in 2017 with the participation of 85 centers. In the study, carditis was reported 84.7%, polyarthritis 54.7%, chorea 25.9%, subcutaneous nodule 8.2%, erythema marginatum 5.9%.[18] In a recent multicenter study, arthritis (52.8%), carditis (53.5%), chorea (7.9%), erythema marginatum (0.36%) were observed, and no subcutaneous nodule was observed.[19] The incidence of major criteria for ARF in our study is similar to the literature.

Among the minor findings, ESR elevation was reported in 81.8%-95%, arthralgia 54.6%-81.1%, fever 40-62%, PR interval prolongation 15.8%-23%, and CRP elevation was reported in 72-81.8% of ARF patients.[20] In the retrospective studies of

Orun et al. from our country between 1980 and 2009, it was reported that CRP elevation was in 71.2%, ESR elevation was in 87.3%, fever 41.5%, arthralgia 60.6%, and PR prolongation was found in 15.8% of ARF patients.[21] PR prolongation was found in 20% of the patients in the study of Karacan et al. and in 23% of the patients in the study of Alqanatihs et al.[22,23] In the study conducted by Gungor et al. in 2004-2009, fever (28%), arthralgia (20.6%), PR prolongation (15.2%), ESR elevation (97.5%) and CRP elevation (84.9%) were reported.[16] In the national 2021 study, fever was reported in 33%, prolonged PR interval in 13.2%, monoarthralgia in 1.6%, elevated ESR in 80%, and elevated CRP in 77% of ARF patients.[19] ESR and CRP, which are acute phase reactants, are non-specific parameters for acute rheumatic fever. ESR and CRP are typically elevated in patients with ARF. It is important in monitoring the acute phase of ARF. Of the patients included in our study, 39 (70.91%) had elevated CRP, 54 (98.18%) elevated ESR, 2 (3.6%) had fever, 4 (7.27%) had PR prolongation according to age and heart rate, and monoarthralgia were observed in 15 (27.27%) patients. These findings appear to be comparable to previous studies.

Supporting findings are data proving previous streptococcal infection. The most common supportive laboratory finding is high ASO.[24] In terms of supporting findings in our study, ASO titer was elevated in 48 patients (87.27%), and GAS was observed in 2 (6%) of 33 patients whose throat cultures were taken. The rate of cases with high ASO was similar to the literature. The low positivity in the throat culture of the patients is thought to be related to their previous use of antibiotics due to upper respiratory tract infections.

Echocardiographic examination has been of great importance for years in the diagnosis, treatment response and long-term follow-up of acute rheumatic fever. It is a frequently used diagnostic method because it is non-invasive, accessible, and practical. EF and FS measurements are standard methods for evaluating left ventricular systolic function. The diagnosis of subclinical carditis is also accepted as a major finding in the 2015 updated Jones criteria. Echocardiography plays a major role in the diagnosis of subclinical carditis in patients without a murmur on auscultation.[6] The relationship between corticosteroid and myocardial hypertrophy was first described by Alpert in a 14-month-old patient, and it was observed that cardiac pathology regressed, and ECHO findings returned to normal with steroid reduction.[25] Miranda-Mallea et al., on the other hand, reported that corticosteroids can cause hypertension, and hypertension results in hypertrophy directly in the heart muscle.[26] There has been a direct correlation between aldosterone levels and LVM in patients with chronic renal failure.[27] LVM and LVMI have not been previously studied in ARF patients in the literature. In our study, no significant difference was found when LVM and LVMI were compared before and after treatment. Our findings suggest that steroid therapy does not have a negative effect on cardiac remodeling in the early period in patients with ARF.

Hemogram, inflammation parameters and rates have been evaluated by studies conducted in various diseases over time, as well as their routine use.[28] In a study by Sert et al., which included 40 patients and 40 healthy groups, there was no significant difference between the two groups in terms of platelet and MPV values, while there was a significant increase in WBC counts when the patients with ARF were compared after diagnosis and treatment.[19] Compared to the healthy control group, a statistically significant increase in WBC and platelet counts, and a significant decrease in MPV values were found in the acute attack of patients with ARF.[19] In their study, Sert et al. reported that the decrease in MPV value in ARF patients in acute attack caused the inhibition of megakaryopoiesis as a result of excessive production of proinflammatory cytokines and acute phase reactants, and this caused the release of small-sized platelets from the bone marrow.[19] Previously reported studies have shown that IL-6 causes an increase in platelet count and a decrease in MPV values.[29] In a study conducted by Aşık et al., in which 50 patients with ARF and 50 control groups participated, a statistically significant difference was found, with WBC, neutrophil count, neutrophil/lymphocyte count ratio, and platelet high in the case group, while lymphocyte, hemoglobin, and MPV were high in the control group.[30]

In the literature, SII and L/CRP has not yet been studied in patients with ARF. In our study, when the laboratory values of the patients were examined, it was determined that WBC, PLT, MPV, NE, PCT, MCHC, MO, CRP, ESH, NLR, NMO, TLO, EO, and SII values decreased significantly after treatment, while MCH, RDW, PDW, L/CRP values increased significantly after treatment.

When the studies on the correlation analysis of acute phase values of ARF patients were examined, it was seen that there was a correlation between the neutrophil/lymphocyte ratio and WBC, sedimentation, and CRP values in the ARF study of Çelik et al.[31] On the other hand, Giray et al. reported a positive correlation between platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio and ESH and CRP values.[32] In their study, Sert et al. reported a negative correlation between ESR, WBC, MPV and PLT in the correlation analysis of acute phase values before treatment.[19]

In our study, the correlations between pre- and post-treatment values of hemogram and inflammation parameters and MPV, SII were examined. Pre-treatment MPV and pre-treatment TLR, LMO, pre-treatment MPV and post-treatment CRP were negatively weak, MPV/L positively moderate, pre-treatment SII and WBC, NLR, NE were positively high, TLR was moderately positive correlation was determined. We believe that these parameters, which are simple, applicable and easily accessible, may be useful for the follow-up of inflammation in ARF.

Limitations

Due to the retrospective nature of our study, there are certain limitations. Limitations such as the fact that patient data

were obtained from the file records and the patients received different treatments may also have affected our results. The accuracy of our findings can be confirmed by examining more patients in larger studies in the future. Despite these limitations, we believe that our study will contribute to the literature thanks to its previously unpublished findings.

CONCLUSION

The clinical findings of our ARF patients are comparable to the literature data. In our study, there was no significant change in LVM and LVMI values before and after treatment, and we believe that LV remodeling was not affected by treatment. We showed that aortic valve regurgitation was significantly reduced with treatment. Significant changes in inflammatory parameters such as L/CRP after treatment, a positive high correlation between pretreatment SII and WBC, NLR, NE, and a moderate positive correlation between TLR may be an easy and applicable option for the evaluation of inflammation in ARF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selcuk University Local Ethic Committee (Date: 13.11.2019 Decision No: 2019/321).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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