

# Evaluation of Children with Acute Rheumatic Fever: A Single-Center Experience

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## What is already known on this topic?

In some previous studies, the epidemiological characteristics, risk factors, complications, recurrence status, clinical and laboratory features, and treatments of patients with acute rheumatic fever (ARF) were evaluated.

## What this study adds on this topic?

We shared new data on ARF patients both for our region and our country, using the Jones criteria revised by the American Heart Association in 2015. We determined that non-compliance with prophylaxis and living in crowded households increase the risk of developing carditis, the severity of carditis, and the risk of recurrence. We found that alanine aminotransferase was significantly higher in patients with ARF recurrence. In addition, as far as we know, this study is the first study conducted in our country in terms of evaluating patients who were previously evaluated with a pre-diagnosis of ARF and were later diagnosed with a different condition.

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Received: March 1, 2021

Accepted: June 3, 2021

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## ABSTRACT

**Objective:** The epidemiological characteristics, risk factors, complications, recurrence status, clinical and laboratory features, and treatment methods of the patients who admitted to our Pediatric Cardiology Outpatient Clinic with a pre-diagnosis of acute rheumatic fever (ARF) were evaluated.

**Materials and Methods:** The data of 166 patients who admitted with a pre-diagnosis of ARF and were diagnosed with ARF, and the data of 51 patients who were not diagnosed with ARF, were retrospectively analyzed.

**Results:** The patients with ARF were between the ages of 5 and 18. Most of the patients with ARF attack admitted in December (15.6%), January (13.8%), and February (13.2%). The most common complaints of the patients diagnosed with ARF were isolated joint pain and/or swelling, at 50.6%. While 91.5% of the patients were diagnosed for the first time, 8.5% had ARF recurrence. It was seen that the most common major criterion was carditis (94.6%). The severity of valve regurgitation and the rates of monoarthritis were significantly higher in patients with recurrence ( $P < .05$ ). Non-compliance with prophylaxis was observed in 10 (71.4%) of 14 patients with recurrence, and in 43 (28.2%) of 152 patients without recurrence. Anti-streptolysin O was lower ( $P = .021$ ) and alanine transaminase (ALT) was higher ( $P = .019$ ) in the recurrence group.

**Conclusion:** Our study showed that in patients with a pre-diagnosis of ARF, a differential diagnosis should be made with other diseases. Especially in patients with joint complaints as the only major symptom, a differential diagnosis should be made. ARF recurrence is associated with non-compliance with prophylaxis, and both the severity of valve regurgitation and monoarthritis rates are higher in patients who develop recurrence. Alanine aminotransferase is significantly higher in patients with ARF recurrence.

**Keywords:** Acute rheumatic fever, carditis, arthritis, recurrence

## INTRODUCTION

Acute Rheumatic Fever (ARF), is an inflammatory disease that develops a few weeks after a throat infection caused by group A  $\beta$ -hemolytic streptococci, and involves organs such as the heart, joints, and brain, and is based on immune responses. ARF and rheumatic heart disease (RHD) are one of the most important causes of acquired heart diseases in our country and other developing countries, which emerge as a crucial public health problem<sup>1-3</sup> It has been reported that there are approximately 471 000 new ARF patients each year, and the incidence between the ages of 5 and 15 is 10-375 cases per 100 000 (ARF in children ages 5-15 years ranging from 10 cases per 100 000).<sup>4</sup>

**Cite this article as:** Güneş A, Akin A, Türe M, Balık H, bilici M, Gül Ö. Evaluation of children with acute rheumatic fever: A single-center experience. *Turk Arch Pediatr.* 2022;57(1):26-31.

ARF is diagnosed using the Jones criteria, which were revised by the American Heart Association in 2015. To avoid overdiagnosis in low-incidence populations and to avoid underdiagnosis in high-risk populations, the diagnostic criteria that separate the populations as low-risk and high-risk groups have been suggested.<sup>5</sup>

ARF continues to threaten human health, and our study aims to analyze it from the clinical and epidemiological aspects. Our aim is to determine the epidemiological characteristics of ARF and the diseases that can be confused with it, based on the data of the last 5 years obtained from our tertiary hospital providing healthcare to the population of the Southeastern Anatolia Region in Turkey. In this study, the course of valve involvement was also evaluated in the post-diagnosis follow-up. Our study also tried to determine the diseases included in the differential diagnosis, by evaluating the patients with a preliminary diagnosis of ARF but not diagnosed with ARF, unlike similar studies in the literature.

## METHODS

### Patients

Two hundred seventeen patients who admitted to the Pediatric Cardiology Outpatient Clinic between January 1, 2012 and December 31, 2017 with a pre-diagnosis of ARF were included in the study. Patient data were obtained by scanning from patient files and computer records. The final diagnoses of the patients who applied to the Pediatric Cardiology Outpatient Clinic with the pre-diagnosis of ARF were made by scanning prospectively and retrospectively from the computer database, file records, and records of the consultant department. The approval for this study was obtained from the Clinical Research Ethics Committee of Dicle University (08.09.2017/191). Patient data were obtained retrospectively and prospectively.

### Clinical Practice

Our patients were diagnosed with ARF according to the previous Jones criteria until 2015, and the modified Jones criteria revised by the American Heart Association from 2015 (5). The presence of mitral and/or aortic regurgitation without symptoms of cardiomegaly and heart failure was evaluated as mild carditis. Patients with cardiomegaly detected on telecardiography, or with valve regurgitation accompanied by enlargement of cardiac chambers, seen on echocardiography (ECHO), were evaluated as having moderate carditis. Patients with symptoms of heart failure were evaluated as having severe carditis.<sup>5,6</sup>

### Electrocardiographic and Echocardiographic Examination

The 12-lead surface electrocardiogram (ECG) recordings of the patients were reviewed; and if the PR interval on the ECG was above the upper limit of the normal value for that age, a diagnosis of first-degree AV block was made.

The discrimination between pathological and physiological valve regurgitation was made according to the ECHO results.<sup>5</sup> Mitral regurgitation was considered pathological if the following 4 findings were observed on the ECHO evaluation: mitral regurgitation seen through at least 2 echocardiographic windows, jet length  $\geq 2$  cm, peak velocity  $>3$  m/s, and

the presence of a pan systolic jet. Aortic regurgitation was considered pathological if the following 4 findings were observed: aortic regurgitation seen through at least 2 echocardiographic windows, jet length  $\geq 1$  cm, peak velocity  $>3$  m/s, and the presence of a pan diastolic jet.<sup>5</sup>

### Laboratory Examination

Erythrocyte sedimentation rate (ESR)  $\geq 30$  mm/h, C-reactive protein (CRP)  $>0.5$  mg/dL, and antistreptolysin O (ASO) titers  $>300$  Todd Units were considered significant. An axillary temperature of  $38^{\circ}\text{C}$  and above was considered as a fever.

### Statistical Analysis

The Statistical Package for the Social Sciences Version 18.0 for Windows software was used for the statistical evaluation of the data. The conformation of variables to the normal distribution was evaluated with visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov / Shapiro-Wilk test) methods. Descriptive statistics were given using the median for continuous non-normally distributed variables and the mean for normally distributed variables. The frequencies for categorical variables were shown as percentage and ratio. Chi-square or Fisher's tests (in case the values observed in the cells did not meet the chi-square test assumptions) were used to compare categorical variables between the groups. The Student's *t*-test was used for parametric variables, and the Mann-Whitney *U*-test was used for non-parametric variables. Spearman's correlation was used for correlation analysis. A *P* value  $<.05$  was considered statistically significant.

## RESULTS

### Epidemiological Features

While 166 of the 217 patients included in the study were diagnosed with ARF, 51 patients had a different diagnosis. Of the 166 ARF patients, 51.2% were male, whereas 49% of the 51 patients who did not have ARF were male. In 68 (40.9%) patients with ARF, there was consanguinity between the parents. In addition, the mean number of individuals living in the same house with these patients was  $8.54 \pm 0.18$ . The demographic data of the patients with ARF are shown in Table 1. The patients with ARF

Demographic Data	Patients (n = 166)
Age (years)	12.08 $\pm$ 2.7
Gender	
Male	85 (51.2%)
Female	81 (48.8%)
Weight (kg)	42.3 $\pm$ 11.8
Consanguinity between the parents	68 (40.9%)
Place of residence	
City	88 (53%)
District	62 (37.4%)
Village	16 (9.6%)
The number of individuals living in the same house	8.54 $\pm$ 0.18

*n*, number of patients; mean  $\pm$  standard deviation.

admitted most commonly in December (15.6%), January (13.8%), and February (13.2%).

**Clinical and Laboratory Findings**

It was found that the most common complaints of the patients were isolated joint pain and/or swelling, at 50.6%. The complaints of the patients diagnosed with ARF at the time of admission are shown in Table 2. Acute-phase reactants (APR) and the other laboratory parameters of the patients at the time of diagnosis are shown in Table 3. It was seen that the most common major criterion was carditis (94.6%). Among the minor criteria, an increase in the APR (81%) was the most common. APR were normal in 6 out of 7 patients with Sydenham’s chorea and in 25 patients with insidious carditis, while in all the other patients, ESR and/or CRP levels were found to be elevated. The findings in patients with ARF according to the 2015 Revised Jones criteria are shown in Table 4.

In 42 (25.3%) patients with ARF, one major criterion was found at the time of admission; 2 major criteria in 120 (72.3%) patients,

**Table 2.** The Distribution of Complaints in the Patients Diagnosed With ARF at the Time of Admission

	n = 166	%
Joint pain and/or swelling	84	50.6
Joint complaints and other complaints	46	27.7
Joint complaint and fever	32	19.2
Joint complaint and chest pain	6	3.6
Joint complaint, fever, and URTI	5	3
Joint complaint, fever and chest pain	2	1.2
Joint complaint and URTI	1	0.6
Palpitations or chest pain	12	7.2
Fever	1	0.6
Fever and chest pain	1	0.6
Sydenham chorea	7	4.2
Other complaints	15	9

n, number of patients; URTI, upper respiratory tract infection.

**Table 3.** Laboratory Parameters of the Patients With Acute Rheumatic Fever

	ARF (n = 166)
ESR (mm/h)	36.7 ± 16.1
CRP (mg/dL)	7.3 ± 7.5
WBC (10 <sup>3</sup> /μL)	11.1 ± 3.8
BUN (mg/dL)	23.3 ± 8.09
Creatinine (mg/dL)	0.59 ± 0.08
ALT (U/L)	19.1 ± 18.8
AST (U/L)	24.95 ± 19.04
ASO (IU/mL)	1006 ± 1016
RF positivity (IU/mL)	2
ANA positivity	10
Anti-dsDNA positivity	1
Brucella tube agglutination positivity	0
Throat culture positivity	7

n, number of patients; mean ± standard deviation; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; CRP, C-reactive protein; ASO, antistreptolysin O; WBC, white blood cells; RF, rheumatoid factor; BUN, blood urea nitrogen; ANA, anti-nuclear antibody; ALT, alanine aminotransferase.

**Table 4.** The Distribution of Patients With Acute Rheumatic Fever According to the 2015 Revised Jones Criteria

	n = 166	%
<b>Major criteria</b>		
Arthritis (polyarthritis or monoarthritis or polyarthralgia)	127	76.5
Polyarthritis	90	54.2
Monoarthritis	17	10.2
Polyarthralgia	112	67.5
Carditis	157	94.6
Sydenham chorea	7	4.2
Erythema marginatum	3	1.8
Subcutaneous nodule	1	0.6
<b>Minor criteria</b>		
Fever	51	30.7
Monoarthralgia	0	0
First-degree atrioventricular block on the ECG	61	36.7
APR positivity	108	65
Streptococcal infection		
ASO value	128	85.3
Throat culture positivity	7	5.3

n, number of patients; ECG, electrocardiography; ASO, antistreptolysin O; APR, acute-phase reactants.

3 major criteria in 3 (1.8%) patients, and 4 major criteria in 1 (0.6%) patient were found. It was observed that 66 (39.7%) patients had 1 minor criterion, 61 (36.7%) patients had 2 minor criteria, and 18 (10.8%) patients had 3 minor criteria. The difference was significant ( $P < .05$ ). One hundred fifty-seven patients had carditis; mild carditis was detected in 101 (60.9%) patients, moderate carditis in 54 (32.5%) patients, and severe carditis in 2 (1.2%) patients. In patients with carditis, the number of individuals living in the same house was higher ( $10.85 \pm 2.01$  vs.  $5.6 \pm 2.44$ ) ( $P = .021$ ). It was found that as the number of major criteria increased, the severity of carditis increased positively ( $P = .048$ ;  $r = 0.154$ ), and the severity of carditis was higher in patients with poor compliance to treatment ( $P = .031$ ). The severity and frequency of mitral regurgitation and aortic regurgitation according to the first and last ECHO results of the patients are shown in Table 5.

**Table 5.** Rates of Involvement of Patients With Acute Rheumatic Fever on First and Last ECHO Performed

Valve regurgitation	First ECHO		Last ECHO	
	n (166)	%	n (154)	%
No presence of MR	14	8.4	23	14.9
Presence of MR	152	91.6	131	85.1
1. MR	109	65.7	109	70.8
2. MR	34	20.5	14	9.1
3. MR	9	5.4	8	5.2
No presence of AR	90	54.2	89	57.8
Presence of AR	76	45.8	65	42.2
1. AR	68	41	58	37.7
2. AR	7	4.2	7	4.5
3. AR	1	0.6	0	0

n, number of patients; ECHO, echocardiography; MR, mitral regurgitation; AR, aortic regurgitation.

### ARF Recurrence

One hundred fifty-two (91.5%) patients with ARF were diagnosed for the first time, while the remaining 14 (8.5%) patients had an ARF recurrence. Monoarthritis was detected in 10 patients (6.5%) in the first diagnosis group and in 7 patients (50%) in the recurrence group, and the difference was significant ( $P < .05$ ). In the first diagnosis group, the severity of mitral regurgitation at the time of diagnosis was found to be lower ( $1.32 \pm 0.56$  vs.  $1.58 \pm 0.77$ ) ( $P = .019$ ). In addition, the severity of aortic regurgitation was found to be lower in the last ECHO examination of the first diagnosis group ( $1.12 \pm 0.37$  vs.  $1.27 \pm 0.33$ ) ( $P = .031$ ). Non-compliance with prophylaxis (not taking 1 or more doses of prophylactic penicillin) was observed in 10 (71.4%) of 14 patients with recurrence and in 43 (28.2%) of 152 patients without recurrence.

Patients with newly diagnosed ARF and ARF recurrence were compared in terms of the Jones criteria and laboratory findings (blood urea nitrogen, alanine aminotransferase, and aspartate aminotransferase). The frequency of monoarthritis was significantly higher in the ARF recurrence group (10% vs. 50%;  $P < .001$ ). In addition, ASO values were lower in the ARF recurrence group than in the new diagnosis group ( $1043 \pm 1047$  IU/mL vs.  $645 \pm 534$  IU/mL;  $P = .021$ ). Alanine aminotransferase was  $17.9 \pm 17.8$  U/L in the new diagnosis group and  $29.5 \pm 24.7$  U/L in the ARF recurrence group. Although alanine transaminase (ALT) levels were within normal limits, ALT levels were found to be significantly higher in the recurrence group ( $P = .019$ ). There was no significant difference between the 2 groups in terms of the other parameters compared.

### Patients Diagnosed as Non-ARF

The final diagnoses of the 51 patients who admitted with a pre-diagnosis of ARF but were not diagnosed with ARF were as follows: physiological valve regurgitation ( $n = 9$ , 17.6%), juvenile idiopathic arthritis ( $n = 7$ , 13.7%), non-specific arthralgia ( $n = 4$ , 7.8%), acute poststreptococcal reactive arthritis ( $n = 4$ , 7.8%), Brucella infection ( $n = 3$ , 5.9%); Familial Mediterranean Fever ( $n = 2$ , 3.9%), septic arthritis ( $n = 2$ , 3.9%), Behçet's disease ( $n = 1$ , 2%), upper respiratory tract infection ( $n = 1$ , 2%) and Henoch-Schoenlein purpura ( $n = 1$ , 2%). Although 17 (33.3%) patients were referred to our department with a pre-diagnosis of ARF (murmur, frequent tonsillopharyngitis, high ASO, etc.), no pathological findings were observed in either the physical or the laboratory examination.

## DISCUSSION

As a consequence of poor living conditions in socioeconomically disadvantaged and developing regions, the inadequate use of primary healthcare services and non-compliance with the treatment of penicillin prophylaxis, ARF continues to remain relevant and to threaten human health in these regions.<sup>7</sup> Studies show that ARF is also an important public health problem in our country. In a study evaluating ARF patients in the 3 decades between 1980 and 2009 in our country, the incidence rates per 100 000 children were found to be 37.60 and 21, respectively.<sup>8</sup> In a study evaluating the incidence rate of ARF between the years 1998 and 2011, it was determined to be 7.4/100 000.<sup>3</sup> Many studies have reported that ARF is seen in both genders at an equal rate.<sup>8-10</sup> The gender ratio of the patients in our study (male/female, 1.05) was consistent with these studies.

Many studies have determined that joint complaints are the most common complaint.<sup>11</sup> Consistent with these studies, the most common complaint found in our study was isolated joint pain or swelling, with a rate of 50.6%.

In various studies, the major criteria have been found to occur at different frequency rates.<sup>12,13</sup> In some studies, the frequency of carditis in children with ARF have been found to be between 30% and 45%.<sup>7,14</sup> In studies conducted in our country, the frequency of carditis has been reported to be 50-84%.<sup>3,8,15</sup> In our study, the most common major finding was found to be carditis, with a high rate of 94.6%. We believe that the reason for the high rate of carditis is due to the fact that our center, where the study was conducted, is a tertiary hospital, where patients with suspected carditis are referred more frequently; and also that insidious carditis patients were included in the study.

In our study, it was observed that 5.4% of the patients did not have carditis, 60.8% of the cases had mild carditis, 32.5% had moderate carditis, and 1.2% had severe carditis. In a study conducted in the United States, it was reported that the carditis severity rates were 55% mild, 25% moderate, and 20% severe in patients with ARF.<sup>16</sup> In the study conducted by Güler et al.<sup>15</sup> after the guidance was updated in 2015, 95% of the patients with carditis were found to have mild carditis and 5% had moderate carditis.

Karaaslan et al.<sup>17</sup> found mild carditis as 83.2%, moderate carditis as 12%, and severe carditis as 4.8%. In our study, except for the number of individuals living in the same house, no relationship was found between the other parameters such as age and gender and the severity of carditis. In addition, it was observed that the carditis was more severe in patients with poor compliance with treatment. The relationship between the severity of carditis and the above-mentioned 2 conditions (the number of individuals living in the same house and compliance with treatment) that may indicate socioeconomic development, shows the importance of sociodemographic characteristics in terms of the development of both ARF and more severe diseases.

In a previous study conducted in our center by Pirinçioğlu et al., MY was found with a rate of 80.4% and AY was found with a rate of 49% in ARF. Similarly, in our study, the frequency of mitral regurgitation was found as 91.6%. The aortic valve is the second most involved valve in rheumatic carditis.<sup>18</sup> In various studies, the aortic regurgitation frequency has been found to be between 9% and 35%.<sup>9,10</sup> In our study, the aortic regurgitation frequency rate was found to be higher (45.8%) than the previously reported rates. According to the data of a study conducted in our country, isolated mitral regurgitation was found at 45%, and isolated aortic regurgitation was found at 5%.<sup>12</sup> In our study, similar to these rates, they were found at 51.5% and 3.2%, respectively.

While valvular pathologies can be completely cured after acute attack treatment or during the follow-up of patients, in some cases, the regurgitation continues to exist. Erdem et al.<sup>2</sup> reported that 7.5% of the patients with valve regurgitation had complete resolution during follow-up. In our study, on the ECHO that was performed at the end of the follow-up, it was found that the rate of aortic regurgitation went

from 45.8% down to 42.2%. Although the rate of improvement in the frequency of valve regurgitation after treatment seems less compared to the rate in the literature, in our study, the rate of grade 2 mitral regurgitation decreased from 20.5% to 9.1%, and similarly in one of our patients, the severe aortic regurgitation regressed to moderate aortic regurgitation. Although the rates of improvement or regression in valve regurgitation were less than in the literature, we believe that the regression in the valve regurgitation will be more in the long-term follow-up of the patients.

The prevalence of migratory and often polyarticular arthritis has been found to be 50-80% in previous studies in the literature.<sup>7,19</sup> In our study, the second most common major finding was arthritis, at 76.5%, consistent with the literature. In studies conducted in countries where there is a high prevalence of the disease, aseptic monoarthritis with a rate up to 17% in patients with ARF has been reported.<sup>12</sup> The fact that in our study, which was conducted in Turkey where there is a high incidence of ARF, the monoarthritis rate was found consistent with the above-mentioned studies as 10.2%, supports the modified Jones criteria.

In patients with ARF, the most important mechanism in the progression of RHD is the recurrence of rheumatic fever.<sup>20</sup> Poor compliance with prophylaxis has been universally identified as a predisposing factor for the development of recurrent diseases.<sup>21</sup> When we compared the patients who were diagnosed with ARF for the first time and the patients with recurrent ARF, we found that non-compliance with prophylaxis was higher in patients with recurrence. The recurrence rate was found to be 14% in the study conducted by Camara et al.<sup>20</sup> In our study, this rate was found to be 8.4%. In addition, in different studies conducted by Camara et al. it has been shown that mitral involvement is more severe in patients with recurrence.<sup>22</sup> Similarly, in our study, mitral regurgitation at the time of diagnosis was found to be more severe in patients with recurrent ARF when compared with patients who had an initial attack of ARF. However, since the number of patients with recurrence is low, comparing the 2 groups may not provide sufficient information. Therefore, the study findings should be supported with a higher number of patients who have ARF recurrences.

Our study showed that monoarthritis is significantly higher in patients with recurrence. This relationship has not been defined before, and it shows that the presence of monoarthritis should serve as a warning in evaluating the recurrence of ARF. Furthermore, in our study, the higher alanine aminotransferase levels in recurrent ARF may be related to the higher severity of valve involvement in these patients. However, further studies are needed to confirm this relationship.

Many disease tables and clinical situations can be confused with ARF.<sup>23</sup> The most important reasons for the confusion of ARF with these diseases are the similarities in symptoms and increased APR. In our study, joint complaints, which were the most common symptom in patients with ARF, were found to occur at similar rates in the patient group that did not have

ARF (50.6% and 54.9%). In our study, one-third of the patients referred with the pre-diagnosis of ARF were cases with no signs other than ASO elevation, frequent tonsillopharyngitis or murmur. Therefore, family physicians and pediatricians should be advised to that a history of frequent tonsillopharyngitis in a child without other findings or ASO elevation are not always associated with ARF. The other major pathologies that are confused with ARF are diseases with joint complaints; juvenile idiopathic arthritis and acute poststreptococcal reactive arthritis were found to be common causes in our study. It is easy to distinguish between these diseases and ARF joint involvement, by doing a careful study of the history and a physical examination. Therefore, physicians should pay attention to differential diagnosis.

In order to illuminate the real incidence of ARF in our country, the differences between the regions, and the deficiencies in the studies, it is necessary to conduct studies with high participation rates throughout the country. Due to the fact that the high frequency of ARF is related to the inadequate treatment of ABHS infections, both in this regard and in order to minimize recurrences, increase compliance with treatment and give correct treatment, it is necessary to raise patient and physician awareness.

## CONCLUSION

Acute rheumatic fever (ARF) continues to be a major health problem. It is more common in the winter, and it is seen in both genders at a similar rate. ARF recurrence is associated with non-compliance with prophylaxis, and both the severity of valve regurgitation and monoarthritis rates are higher in patients who develop recurrence.

Alanine aminotransferase is significantly higher in patients with ARF relapse. However, although ALT is high, it is still within normal limits, and further studies are needed to confirm this relationship. No pathology was found in one-third of the patients who were referred to a pediatric cardiologist with a pre-diagnosis of ARF and were not diagnosed with ARF. The most common diagnoses in this group are physiological valve insufficiency and juvenile idiopathic arthritis. Whether the valve regurgitation, which is detected using ECHO, is pathological or not should be accurately determined; and especially in patients with joint complaints as the only major symptom, an elaborate differential diagnosis should be made.

## Take-Home Messages

ARF is an important health problem for our country. The frequency of carditis is high in these patients. In patients with poor compliance with prophylaxis, the severity of ARF recurrence and valve involvement increase. Therefore, patients should be informed about adherence to prophylaxis. It should be known that ARF cannot be diagnosed with frequent tonsillopharyngitis or high ASO without other findings.

## Limitations of the Study

This study has some limitations since it is retrospective. The fact that some of the patient data may have been missing due to the inadequacies in the medical records system should be

taken into consideration. Another limitation of the study is that the prognosis of RHD could not be demonstrated with a long-term clinical follow-up.

**Ethical Committee Approval:** The approval for this study was obtained from the Clinical Research Ethics Committee of Dicle University (08.09.2017/191).

**Informed Consent:** Informed consent was obtained from all individual participants included in the study.

**Peer review:** Externally peer-reviewed.

**Author Contributions:** Concept – A.G., M.T.; Design – M.T., A.A.; Supervision – H.B., M.B.; Resources – Ö.G., M.T.; Materials – A.G., A.A.; Data Collection and/or Processing – H.B., Ö.G.; Analysis and/or Interpretation – A.A., M.B.; Literature Search – A.G., Ö.G.; Writing Manuscript – M.T., M.B.; Critical Review – M.T., A.A.

**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.

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