North Clin Istanb 2023;10(2):237–247
doi: 10.14744/nci.2021.58966

ORIGINAL ARTICLE PEDIATRICS

Changing face of acute rheumatic fever in childhood and our clinical results

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ABSTRACT

OBJECTIVE: This study aims to evaluate the demographic and clinical findings of acute rheumatic fever (ARF) patients followed up in our clinic, their responses to treatment, and prognoses and to determine the clinical utility of echocardiography (ECHO) in the diagnosis of ARF.

METHODS: We retrospectively evaluated the data of 160 patients with ARF (6–17, mean 11.7±2.3 years, F/M: 88/72) that was diagnosed according to the Jones criteria and followed up in the pediatric cardiology clinic between January 2010 and January 2017.

RESULTS: About 29.4% (n=47) of 104 patients with rheumatic heart disease (RHD) had subclinical carditis. It was observed that subclinical carditis was most common in patients with polyarthralgia (52.2%); in contrast, clinical carditis was most commonly observed together with chorea (39%) and polyarthritis (37.1%). It was found that 60% (n=96) of the patients with rheumatic fever were between the ages of 10–13 and 31.3% (n=50) presented arthralgia most frequently in the winter months. The most common concomitant major symptoms were carditis + arthritis (35%) and carditis + chorea (19.4%). In patients with carditis, the most affected valves were mitral (63.8%) and aortic (50.6%) valves, respectively. The prevalence of monoarthritis, polyarthralgia, and subclinical carditis increased in cases diagnosed during and after 2015. The cardiac valve involvement findings of 71 of 104 patients (68.2%) with carditis improved during the approximately 7 years of follow-up. The regression of heart valve symptoms was significantly higher in patients with clinical carditis and those that complied with prophylaxis compared to patients with subclinical carditis and those that did not comply with prophylaxis.

CONCLUSION: We conclude that ECHO results should be included in the diagnostic criteria of ARF, and that subclinical carditis is associated with a risk of developing permanent RHD. Secondary prophylaxis non-compliance is significantly associated with recurrent ARF, and early prophylaxis can reduce the prevalence of RHD in adults and potential associated complications.

Keywords: Arthritis; carditis; child; echocardiography; rheumatic fever.

Cite this article as: *Erzurumlu Yavrum B, Kibar Gul AE, Azak E, Gursu HA, Cetin II. Changing face of acute rheumatic fever in childhood and our clinical results. North Clin Istanb 2023;10(2):237–247.*

Rheumatic heart disease (RHD) continues to be important public health concerns in several global regions, but particularly in developing countries including Turkiye [1–3]. Three hundred thousand new cases of RHD are identified each year and rheumatic carditis account for 233,000 deaths annually [4–7]. The latest

Received: March 29, 2021 *Revised:* April 28, 2021 *Accepted:* August 26, 2021 *Online:* April 18, 2023

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Jones criteria (2015) defined different diagnostic criteria for moderate- and high-risk populations such as Turkiye [2]. Low-risk areas, by this definition, have an acute rheumatic fever (ARF) incidence of <2/100,000 school-aged children or an all-age rheumatic heart prevalence of <1/1000 persons. According to these criteria, clinically manifested carditis as well as subclinical carditis, as detected by echocardiography (ECHO), are major diagnostic criteria while a fever of 38.5°C is accepted as a minor criterion for low-risk populations, and aseptic monoarthritis and polyarthralgia are accepted as major criteria and monoarthralgia a minor criterion for high-risk populations in higher-risk area [2, 3].

Carditis is the only finding of ARF that can lead to permanent disability [8]. Subclinical carditis can be detected during the first ARF attack of patients with isolated rheumatic chorea or isolated migratory polyarthritis which can be detected by ECHO [8–11]. Different studies report the prevalence of subclinical carditis to be 14–35% [11, 12]. If ECHO is not used, the diagnosis of these patients can be overlooked and may cause recurrent attacks and more severe and early RHD since the patients will not receive secondary prophylaxis. Therefore, the diagnosis of subclinical carditis is crucial due to possible morbidity [13].

This study aims to evaluate the demographic and clinical findings of patients with ARF or RHD followed up in our clinic, their responses to treatment, and prognoses and to determine the clinical utility of ECHO in the diagnosis of ARF. Our results are significant in that they can guide clinicians to develop an approach for the treatment of rheumatic fever and help them combine their evaluations with the diagnostic criteria put forward in our country, where RHD is common, to make correct diagnoses.

Highlight key points

- Subclinical carditis is at risk for persistent RHD.
- The prevalence of monoarthritis and polyarthritis was significantly increased after 2015.
- Subclinical carditis was most common in patients with polyarthralgia, followed by patients with chorea, patients with monoarthritis (n=5, 29.4%).
- Combined valve involvement and accompanying artirit and/or chorea significantly increase the possibility of developing RHD-related sequelae.

MATERIALS AND METHODS

We retrospectively evaluated the files of 160 patients that were diagnosed with ARF between January 2010 and December 2017 in the pediatric cardiology clinic of our hospital. This study was granted ethical approval by the University of Health Sciences Ankara Clinical Research Ethics Committee of our hospital (2018/110).

Patient Selection

This study is a retrospective analysis of medical records in patients with visiting the polyclinic. A total of 160 patients were included in the study: 125 patients who were examined clinically and with ECHO and diagnosed with ARF according to the Jones criteria for the first time in our clinic and 35 patients that had a history of RHD at the time of admission. Between 2010 and 2014, the patients were diagnosed with ARF according to the 1992 Jones criteria and the 2003 WHO criteria [6, 14]. Between 2015 and 2017, they were diagnosed according to the 2015 Jones criteria [2]. These criteria were not required in patients with chorea. Arthralgia was not accepted as a minor criterion in patients with arthritis, and a prolonged PR interval was not accepted as a minor criterion in patients with carditis. Eighteen patients were excluded from the study due to not meeting the Jones criteria, diagnostic uncertainty, comorbid vasculitis or inflammatory diseases (FMF or other rheumatic diseases), or not coming in for follow-ups. Patients who had penicillin prophylaxis regularly and came to polyclinic controls were considered compatible.

Clinical and Demographic Characteristics

The following data were recorded from patient records: age, gender, month and season of diagnosis, place of admission, complaints at the time of admission, history of upper respiratory tract infection, other known diseases, history of ARF, family history of ARF, family history of consanguinity, and duration of follow-up. In addition, patients' compliance with follow-ups and benzathine penicillin G prophylaxis and the number of recurrent attacks (recurrence and reactivation) during follow-up were also evaluated. The following systemic examination results of the subjects were recorded: fever, heart rate, blood pressure, cardiovascular examination, arthritis (monoarthritis, polyarthritis), erythema marginatum, dermatological examination for subcutaneous nodules, and neurological examination for Sydenham's chorea. A fever was defined as having an axillary temperature of 38°C and above, as recorded in patients' files.

The following laboratory examination results were recorded: hemogram, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-streptolysin O (ASO), anti-DNase, and liver function tests. CRP>5 mg/dL, ASO>250 Todd units, and a sedimentation rate >30 mm/h were considered as clinically significant. A white blood cell count above 10000/mm3 was evaluated to indicate inflammation. The throat swab culture results studied in the microbiology laboratory were also recorded. The subjects underwent 12-lead ECG to determine any accompanying rhythm disorders and their PR intervals.

Rheumatic fever patients that were followed up for at least 1 year after their first rheumatic attack and had had available admission and follow-up ECHO findings were included in the comparison. Recurrent attacks were evaluated under two categories: (1) Recurrence: A new ARF attack that resulted from a Group A streptococcal infection that occurred 8 weeks after the end of treatment, (2) Reactivation attack: Cases of relapse where clinical and laboratory findings indicated activation while anti-inflammatory therapy was still in progress and cases of rebound, where the ARF symptoms reappeared 4-6 weeks after the end of treatment [15].

ECHO Examination

All the subjects underwent ECHO, which was performed by a pediatric cardiologist. The patients were examined using the standard protocols defined by the American Heart Association for the echocardiographic examination of pediatric patients without sedation in the supine position using the Vivid 7 Pro (General Electric, Horten, Norway) device with a 3 MHz probe and Philips iE33 (The Netherlands) with a X5-1 transducer. M-mode, standard CW Doppler, PW Doppler, and color Doppler ECHO images were obtained. Mitral regurgitation (MR) jet was evaluated using apical four-chamber view during systole and aortic valve regurgitation jet was evaluated using apical five-chamber view during diastole [14–16].

ECHO results were used to diagnose rheumatic carditis according to the previously described criteria that were approved by the WHO expert committee [17]. Patients that were determined to have valvular regurgitation through ECHO but without audible murmurs were diagnosed with "silent carditis" or "subclinical carditis." Patients with carditis were evaluated as follows: (a) Mild carditis: Patients with murmurs as the only cardiac symptom or those diagnosed with grade 1 valvular regurgitation in ECHO without accompanying cardiomegaly, (b) moderate carditis: Patients that were diagnosed with grade 2 valvular regurgitation in ECHO, and (c) severe carditis: Patients that had symptoms of cardiac insufficiency or were diagnosed with grade 3 or 4 valvular regurgitation in ECHO.

Statistical Analysis

Data were analyzed using SPSS computer package program version 22.0 (the Statistical Package for the Social Sciences, SPSS Inc., Chicago, USA). The descriptive statistics were presented as numbers and percentages for categorical variables and as mean±Standard deviation and median (minimum-maximum values) for continuous variables. The compliance of continuous variables with normal distribution was evaluated using visual (histogram and probability graphs) and analytical (Kolmogorov–Smirnov and Shapiro–Wilk tests) methods. The continuous variables were determined not to have normal distribution. Mann–Whitney U-test was used for the pairwise comparison of non-normally distributed data. The Chi-square test was used to determine whether the subject groups were different in terms of categorical variables. In this study, $p<0.05$ was accepted as statistically significant.

RESULTS

Clinical and Demographic Characteristics

One hundred and sixty subjects were diagnosed with ARF in our clinic within approximately 7 years. Eighty-eight (55%) of these patients were female and 72 (45%) were male. The mean follow-up duration was 3.0±1.9 years (1–6). The mean age at the time of diagnosis was 11.7±2.3 years (6–17 years), and 60% of the patients (n=96) were diagnosed between the ages of 10 and 13. About 78.1% (n=125) of the 160 patients were diagnosed with a first rheumatic fever attack and 21.9% (n=35) had a history of rheumatic carditis. The majority of the patients applied during winter months (n=50, 31.3%) followed by summer (n=45, 28.1%), spring (n=44, 27.5%), and fall (n=21, 13.1%). The most common complaints of admission were arthralgia (71.9%), arthritis (54.3%), and involuntary movements (25%). Other complaints included fever, shortness of breath, chest pain, and palpitations, in order of frequency (6.3%, n=11). During admission, 13 patients (8.1%) had non-

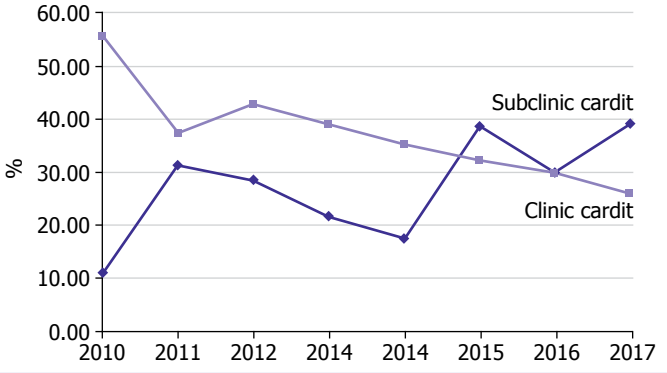

FIGURE 1. Clinical and subclinical carditis incidence by year.

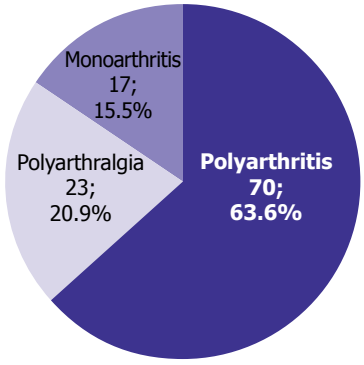

FIGURE 2. The characteristic distribution ARF arthritis.

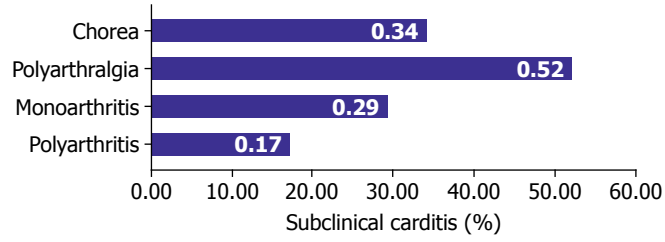

FIGURE 3. Distribution of subclinical carditis according to major findings.

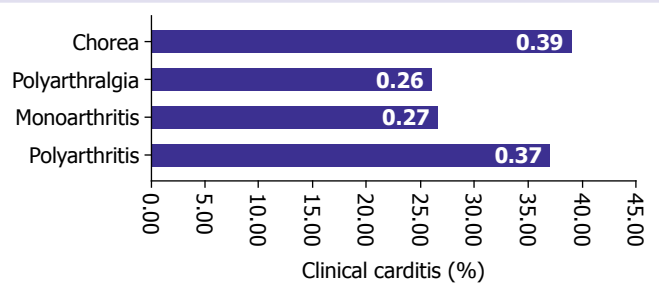

FIGURE 4. Distribution of clinical carditis according to major findings.

ARF-related symptoms (headache, dizziness, syncope, and abdominal pain). About 68.8% (n=110) of the cases had a history of the upper respiratory tract infection and the mean latent period (excluding patients with chorea) was 3.2±1.1 weeks.

The mean heart rate of the subjects was 89.7±13.2 bpm (65–140). Cardiac examination revealed afebrile tachycardia in 17 patients (10.6%) and heart murmurs in 54 patients (33.7%). About 75% of all patients (n=120) had elevated acute phase reactants (APR). The mean sedimentation rate was 64.7±33.0 mm/h (2–132), and the mean CRP level was 6.2±5.9 mg/dL (0.02–26.7). About 99.3% (n=158) of the patients were ASO-positive with a mean ASO value of 966.3±807.1 IU/mL (209–5730). Nine patients (5.6%) had a positive throat culture for Group A beta-hemolytic streptococci. Three patients were tested for anti-DNase and two of these patients were anti-DNase-positive.

Regardless of the year of diagnosis, 39.4% (n=63) of the subjects met the 2015 Jones criteria. About 60.6% (n=97) were diagnosed according to 1992 Jones and 2003 WHO criteria. About 41.3% (n=26) of the 63 patients that conformed to the latest Jones criteria were diagnosed before 2015, and 58.7% (n=37) during or after 2015. The number of patients diagnosed with ARF significantly increased with the new diagnostic criteria (p=0.015). In addition, according to the year also was no significant difference in the distribution of rheumatic carditis (Fig. 1).

Distribution of Major and Minor Findings

The distribution of major and minor rheumatic fever findings at the time of diagnosis is presented before and after 2015 (Table 1). The prevalence of rheumatic carditis (n=104) was significantly higher in females (61.5%) than males (38.5%) (p=0.035). The most common major clinical findings were carditis (65%, n=104) and arthritis and arthralgia (68.7%, n=110). Seventy of the 110 patients with arthritis and/or arthralgia (63.6%) had polyarthritis, 23 (20.9%) had polyarthralgia, and 17 (15.4%) had monoarthritis (Fig. 2). The prevalence of arthritis had significantly increased after 2015 compared to patients diagnosed before 2015, whereas the prevalence of chorea significantly decreased (p<0.01). The incidence of subclinical carditis also increased after 2015, but there was no statistical significance (p=0.202).

Table 1. Distribution of major and minor acute rheumatic fever findings before and after 2015

Parameters	<2015 n=85 (53.1%)		≥2015 n=75 (46.9%)		p
	n	%	n	%	
Major findings at the time of diagnosis					
Total arthritis/arthralgia (n=110, 68.7%)					
1- Arthritis (n=87, 54.3%)	41	48.2	46	61.3	<**0.001**[1]
Polyarthritis	34	40	36	48	
Monoarthritis*	7	8.3	10	13.3	
2- Polyarthralgia* (n=23,20.9%)	6	7.1	17	22.6	
3- Carditis (total, n=104,65%)	54	62.4	50	66.7	0.570[2]
Clinical carditis	34	40.0	23	30.7	0.20[2]
Subclinical carditis*	20	23.5	27	36.0	
4- Chorea	35	42.2	6	8.0	<**0.001**[1]
Minor findings at the time of diagnosis					
Monoarthralgia	16	19.0	21	28.0	0.252[1]
Fever	10	11.9	16	21.3	0.165[1]
Prolonged PR interval	9	10.7	20	26.7	**0.017**[1]
Elevated APR	52	61.9	68	90.7	<**0.001**[1]

APR: Acute phase reactants; Prolonged PR interval: PR>200 msn; 1: Continuity-corrected Chi-square test; 2: Pearson's Chi-square test; *: According to the 2015 Jones criteria, monoarthritis and polyarthralgia are used as major criteria and monoarthralgia is a minor criterion (after excluding other causes).

The most common concomitant major symptoms were carditis+arthritis (n=56, 35%) and carditis + chorea (n=31, 19.4%). When evaluated for carditis severity, there were 47 cases of mild (45.2%), 47 cases of moderate (45.2%) and 10 cases of severe carditis (9.6%). In patients with carditis, the most affected valves were mitral (63.8%) and aortic (50.6%) valves, respectively. At the time of diagnosis, 71 patients (44.4%) had combined aortic and MR and 30 patients (18.8%) had isolated MR.

According to the valve involvement of patients with monoarthritis and polyarthralgia. Was not found statistical difference in the rheumatic heart findings and treatment follow-up (p>0.05) (Table 2). Sixteen of these patients were diagnosed with RHD by adding subclinical carditis to the diagnostic criteria.

It was observed that subclinical carditis was most common in patients with polyarthralgia (n=13, 52.2%); in contrast, clinical carditis was most commonly observed together with chorea (n=16, 39%) and polyarthritis (n=26, 37.1%), (Fig. 3, 4).

Rheumatic Valve Involvement Findings during Treatment and Follow-up and Prophylaxis

The distribution of anti-inflammatory therapy in patients with clinical and subclinical carditis is presented Table 3. Steroid drugs were significantly more commonly used for the treatment of clinical carditis and non-steroidal anti-inflammatory drugs (NSAIDs) were the most preferred drug for the treatment of subclinical carditis (p<0.001). About 23.1% (n=37) of the patients with moderate and severe carditis were treated by hospitalization. Treatment response rate was high for patients with clinical (n=54, 94.6%) and subclinical carditis (n=44, 93.6%) (p<0.05). Surgical valve repair was performed in two patients (1.3%) with severe valve regurgitation during their follow-up. Although the rate of rheumatic heart finding was found to be 85.4% (n=41) in the group that non-steroidal treatment, it was found to be 40.2% (n=41) in the group receiving steroid treatment, but no statistically significant difference was found (p>0.05). The rate of side effects was significantly higher in patients treated with salicylate (n=6) compared to other NSAIDs (n=1) (p=0.001).

Table 2. Rheumatic heart findings and treatment distribution in follow-up according to valve involvement in patients with monoarthritis and polyarthralgia

Parameters	Monoarthritis n=17 (15.4%)		Polyarthralgia n=23 (20.9%)	
	n	%	n	%
No carditis	8	47	6	24
Subclinic cardit	4	26.7	12	52.2
Clinic cardit	4	26.7	6	26.1
Mild cardit	4	26.7	12	52.2
Moderate-severe cardit	4	26.7	6	26.7
isolated mitral regurtation	1	6.7	5	21.7
Mitral and aortic regurgitations	7	46.7	13	56.5
Rheumatic heart finding improved				
Exists	5	62.5	15	83.3
Absent	3	35.7	3	35.7
Persistent rheumatic heart finding				
Exists	8	53.3	16	64
Absent	7	46.7	9	36
Treatment				
Naproxen	9	52.9	13	52
Salicylate	2	11.8	2	8
Steroid	6	35.3	9	36
Compliance with prophylaxis				
Exists	16	94.1	21	84
Absent	1	5.9	4	16

Table 3. The distribution of anti-inflammatory therapy in cases of carditis

Parameters	n	%*
Anti-inflammatory theraphy		
NSAID	56	35.0
Salicylate	3	1.9
Steroid+Naproxen	46	28.8
Steroid+Salicylate	5	3.1
NSAI+Salicylate	13	8.1
Steroid+Salicylate+Naproxen	4	2.6

*: Column percentage is used; NSAID: Non-steroidal anti-inflammatory drugs.

Table 4. Rheumatic heart finding in follow-up according to the degree of carditis

	Mild cardit		Moderate cardit		Severe cardit		p
	n	%	n	%	n	%	
Follow-up rheumatic heart disease*							<0.01[1]
Exists	33	40.7	39	48.2	9	11.1	
Absent	11	68.7	5	32.3	0	0	

1: Pearson's Chi-square test; *: Row percentage is used.

During the follow-up, the findings of rheumatic carditis regressed in 16 patients, 11 of them (68.7%) had mild carditis, and 5 (31.3) had moderate carditis. None of the patients that developed severe carditis had a full recovery. Persistent RHD was found to be significantly lower in cases with mild carditis than patients with moderate and severe carditis during follow-up (Table 4).

In terms of heart valve involvement, 74.5% (n=41) of the patients with clinical carditis had combined AR and MR and 25% (n=14) had isolated MR, whereas these rates were 63.8% (n=30) and 34% (n=16) for subclinical carditis, respectively. The two groups were not statistically different in terms of heart valve involvement (p=0.329). Rheumatic carditis had regressed significantly more in patients with clinical carditis (83.3%) compared to patients with subclinical carditis (55.6%) (p=0.005).

Thirty-seven patients (77.1%) developed reactivation an average 4.1±1.8 weeks after the first attack. In contrast, clinical carditis (74%, n=20) was significantly more common in patients that developed reactivation compared to subclinical carditis (26%, n=7) (p=0.019). The majority of these patients had combined valvular regurgitation 77.8% (n=21) and only 22.2% (n=6) had isolated valve regurgitation. Although clinical carditis and combined valvular regurgitation were significantly more common among patients that developed recurrent attacks (p:0.019). About 4.3% (n=2) of the patients that initially presented with isolated arthritis had developed RHD during follow-ups, whereas none of the patients that presented with isolated chorea (n=11) developed carditis.

During the approximately 7 years of follow-up (an average of 36±22.8 months), a development in valve findings was observed in 71 (68.2%) of 104 patients with rheumatic carditis. Among these patients, the valve involvement regressed in the 1st year for 70.4% (n=50), in the 2nd year for 11.3% (n=8), in the 3rd year for 11.3% (n=8), in the 4th and 5th years for 2.8% (n=2), and in the 6-year follow-up for 4.2% (n=3). Follow-up rheumatic

Table 5. Comparison of aortic regurgitation statuses at the time of admission and during follow-up

Aortic regurgitation involvements in initial echocardiography results*	Aortic regurgitation involvements in final follow-up echocardiography results											
	No significant regurgitation		Trace		Grade 1		Grade 2		Grade 3		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
No significant regurgitation	79	98.8	1	1.2	0	0	0	0	0	0	80	100
Trace	20	64.5	11	35.5	0	0	0	0	0	0	31	100
Grade 1	19	55.9	8	23.5	6	17.6	1	2.9	0	0	34	100
Grade 2	0	0	0	0	3	50.0	2	33.3	1	16.7	6	100
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0

*: Indicates row percentages.

Table 6. Comparison of mitral regurgitation statuses at the time of admission and during follow-up

Mitral regurgitation involvements in initial echocardiography results*	Mitral regurgitation involvements in final follow-up echocardiography results											
	No significant regurgitation		Trace		Grade 1		Grade 2		Grade 3		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
No significant regurgitation	53	98.2	1	1.8	0	0	0	0	0	0	54	100
Trace	9	45	11	55	0	0	0	0	0	0	20	100
Grade 1	5	20	11	44	9	36	0	0	0	0	25	100
Grade 2	5	11.6	16	37.2	16	37.2	6	14.0	0	0	43	100
Grade 3	0	0	0	0	3	33.3	4	44.4	2	22.2	9	100

*: Indicates row percentages.

carditis was found significantly lower in the isolated MR cases (18%) compared to the cases with combined valvular regurgitation (50%) (p=0.024). In patients with carditis, developing RHD was significantly more likely for patients that had accompanying arthritis and chorea compared to patients that had isolated carditis (p<0.01). In addition, valve stenosis was not detected in the follow-up.

Mitral valve involvement statuses at the time of admission and during follow-up are presented in Table 5. Valve regurgitation completely regressed in 45% of the patients that presented with trace MR, and this rate was as low as 11.6% according to the severity of regurgitation. Aortic valve involvement statuses at the time of admission and during follow-up are presented in Table 6. The valvular regurgitation findings completely regressed in the majority of the patients that initially presented with mild AR (64.5% and 55.9%).

Initial and follow-up ECHO findings of 47 patients with subclinical carditis are presented in Table 7. During 6 years of follow-up, the valvular involvement symptoms persisted in 22(46.8%) of 47 patients.

All the patients were given benzathine penicillin G every 3 weeks prophylaxis. The mean prophylaxis period during our follow-up period was 3.2±1.9 years (1–7 years). About

Table 7. Echocardiography follow-up results of the 47 patients with subclinical carditis

	Mitral regurgitation		Aortic regurgitation		Mitral regurgitation/ Aortic regurgitation		No significant regurgitation		Total
	n	%	n	%	n	%	n	%	
At the time of diagnosis	16	34.0	1	2.1	30	63.8	0	0	47
After 6 months	14	29.8	1	2.1	24	51.0	8	17.0	47
After 1 year	12	25.6	1	2.1	18	38.3	16	34.0	47
After 2 years	9	19.1	1	2.1	15	31.9	22	48.6	47
After 3 years	9	19.1	1	2.1	13	27.7	24	51.1	47
After 4 years	9	19.1	1	2.1	13	27.7	24	51.1	47
After 5 years	9	19.1	1	2.1	13	27.7	24	51.1	47
After 6 years	8	17.0	1	2.1	13	27.7	25	53.2	47

Table 8. The relationship between recurrent attacks and compliance with prophylaxis

	Compliance with prophylaxis*				
	Exists		Absence		p
	n	%	n	%	
Recurrence	7	5.5	4	23.5	**0.027****
Non-recurrence	120	94.5	13	76.5	
Regression of rheumatic heart findings					**0.035****
Exists	68	69.4	4	33.3	
Absent	30	30.6	8	66.7	

*: Column percentage is used; **: Fisher Chi-square test.

88.8% (n=142) of the patients complied with prophylaxis. The recurrence rate was 23.5% for non-compliant and 5.5% for compliant patients (p=0.027). Furthermore, the regression of rheumatic heart findings was significantly higher in prophylaxis-compliant patients (69.4%) compared to non-compliant patients (33.3%) (p=0.035) (Table 8).

DISCUSSION

The widespread use of ECHO in the clinical evaluation of rheumatic carditis has gradually increased its significance in the diagnosis of ARF over the years, and an expert consensus has been reached regarding the concept of subclinical carditis [2, 7, 17]. In our study, due to the routine use of ECHO in patients with suspected ARF, we were able to determine that the prevalence of carditis, and especially subclinical carditis, had increased, and that these patients had an increased risk of developing permanent rheumatic heart finding. Another remarkable finding is that the number of ARF patients that were diagnosed due to polyarthralgia and monoarthritis significantly increased after 2015 (p<0.05).

Although rheumatic fever frequently affects patients aged between 5 and 15, studies report ARF attacks in patients aged 2–45 years [7, 18–20]. In our study, the mean age of the subjects was 11.7±2.3 years, and 60% were aged 10–13. The female-to-male ratio was 1.22. Similar to the literature, the majority of the patients presented in winter (31.3%) and spring (27.5%), when infections are more common [18, 20–25]. The literature reports different prevalences for different minor findings such as 54.6–81.1% for arthralgia, 40–62% for fever, 15.9–23% for prolonged PR interval, 81.8–95% for elevated ESR, and 72–81.8% for elevated CRP [26, 27].

Several studies report different frequencies of major ARF findings, evaluated either individually or together. Some studies report that carditis is the most common major finding with a rate of 68.8%, while other studies indicate that arthritis has the first place with 59–57.6%, and other studies report carditis and arthritis concomitance [21–23]. With the increasing prevalence of ECHO in Turkiye, studies started to report increasing rates of carditis in the range of 64–82% [11, 24–26]. Similarly, in our study, carditis and arthritis (35%) were the most common concomitant major findings (Table 1).

The latest Jones criteria (2015) specify that for moderate- and high-risk populations like Turkiye, migrating polyarthritis, aseptic monoarthritis, and/or polyarthralgia are accepted as major criteria [2]. In their study, Carapetis et al. [19] reported polyarthritis in 54% of ARF patients, monoarthritis in 17%, and arthralgia without arthritis in 20%. Turkish studies report the prevalence of monoarthritis to be 12.7–33.2% and emphasize the increasing numbers of ARF attacks that present with monoarthritis [20, 27, 28]. In our study, 68.7% (n=110) of the patients had arthritis and/or arthralgia. In addition, our results showed that the prevalence of monoarthritis and polyarthritis, prolonged PR interval, and elevated APR was significantly higher in patients diagnosed during or after 2015 compared to the period before 2015, whereas a significant decrease was detected in chorea (Table 1) ($p<0.05$). Therefore, mild carditis was detected in five of our patients with monoarthritis and 13 of our patients with polyarthritis.

Different studies report various rates for MR (25–96%), AR (9–35%), and combined MR and AR (25–36%) in patients with rheumatic carditis [26, 27, 29]. In this study, the most involved heart valve was the mitral valve (63.8%), in compliance with the literature [2]. At the time of diagnosis, 71 patients (44.4%) had combined AR and MR and 30 patients (18.8%) had isolated MR. One of the factors that adversely affect the course of the disease is a high number of involved heart valves, and increasing carditis severity is associated with an increased number of involved heart valves and an increased likelihood of developing sequelae in the follow-up [7]. According to our study findings, the follow-up permanent rheumatic heart finding was significantly lower in patients with mild carditis (40.7%) than in patients with moderate or severe carditis (59.3%) ($p<0.05$). Furthermore, patients that had carditis accompanied by arthritis±chorea were significantly more likely to develop RHD than patients with isolated carditis ($p<0.01$). We observed this study during the approximately 7 years of follow-up (an average of 36±22.8 months), no significant regurgitation in valve findings was observed in 71 (68.2%) of 104 patients with rheumatic carditis. Consistently with the literature, the heart valve involvement of 70.4% of patients with carditis largely regressed within the first year, but this rate decreased down to 4.2% by the 6th year [30]. The severity of carditis was not found to be significantly associated with rheumatic valve involvement ($p>0.05$). However, patients that had combined valve regurgitation were significantly more likely to develop RHD in follow-up compared to patients with isolated MR (50% vs. 18%) ($p<0.05$). Our results show that combined valve involvement and accompanying artirit and/or chorea significantly increase the possibility of developing RHD-related sequelae.

Due to the increasing significance of ECHO in the diagnosis of ARF, subclinical carditis has been included in latest revision of Jones criteria (2015) as a major criterion for both low- and moderate-and high-risk populations [2, 31–33]. Various studies from Turkiye report the prevalence of subclinical carditis to be 20.1%, 24.3%, and 26.6%, increasing over time [11, 12, 28]. In our study, we found that 29.4% of the ARF patients had subclinical carditis. Even if not statistically significant, the fact that the prevalence of subclinical carditis increased in patients from 2015 to 2017 (30.7%) compared to 2010–2014 (23.5%) supports the significance of the early ECHO examinations in ARF and its inclusion in diagnostic criteria. Another remarkable finding is the high number of ARF patients that were diagnosed with subclinical carditis and polyarthralgia (52%) and monoarthritis (29.4%), also major criteria [2, 31]. In our study, it was observed that subclinical carditis was most common in patients with polyarthralgia (n=13, 52.2%), followed by patients with chorea (n=14, 34.1%), patients with monoarthritis (n=5, 29.4%), and was the least common in patients with polyarthritis (n=12, 17.1%) (Fig. 1).

The factors that determine the prognosis of subclinical carditis are currently unknown. However, it is known that the valve symptoms of the majority of patients with mild MR who receive regular secondary prophylaxis for 5–10 years have improved [27]. Ozdemir et al. [11] and Ozkutlu et al. [13] observed in their study that 42.5% and 45% of the cases with subclinical carditis developed persistent valve regurgitation, respectively. Similarly, we observed that RHD regression was significantly lower in patients with subclinical carditis (55.6%) compared to patients with clinical carditis (83.3%) over approximately 7 years of follow-up ($p=0.005$). This indicates that patients with subclinical carditis are at risk for persistent rheumatic heart finding.

Rheumatic fever progresses in the form of recurrent attacks and these attacks are largely responsible for permanent RHD. Patients that received regular secondary prophylaxis were found to have a lower recurrence rate compared to those who did not [20, 34]. In this study, 30% (n=48) of ARF patients developed recurrent attacks. Although clinical carditis and combined valvular

regurgitation were significantly more common among patients that developed recurrent attacks ($p<0.05$). Our results showed that the recurrence rate was detected significantly lower in prophylaxis-compliant patients (5.5%) than non-compliant patients (23.5%) ($p<0.05$). Furthermore, the regression of RHD findings was significantly higher in prophylaxis-compliant patients.

Limitation of Our Study

The main limitation of our study is the inclusion of patients that had available follow-up data and the insufficient number of subjects due to incomplete patient files. Further multi-centered studies, particularly from Turkiye, are needed to better understand the clinical prognosis and final outcomes of the patients and to obtain more conclusive results about rheumatic valve involvement and especially the follow-up of patients with subclinical carditis, monoarthritis, and polyarthralgia, whose numbers have increased due to the increasing prevalence of ECHO.

Conclusion

In our study, it is remarkable that the association of subclinical carditis cases with polyarthritis and monoarthritis was significantly high. Due to the routine use of ECHO in patients with suspected ARF in our clinic, it has been determined that the frequency of carditis and especially the number of cases with subclinical carditis has increased in all years and the cases with subclinical carditis have a risk of permanent rheumatic heart finding. It was an important determining factor in the recurrent ARF which is non-compliance with secondary prophylaxis. Hence, the early detection of subclinical carditis and early secondary prophylaxis may contribute to reducing the prevalence of RHD in adults.

Ethics Committee Approval: The University of Health Sciences Ankara Clinical Research Ethics Committee granted approval for this study (date: 25.06.2018, number: 2018-110).

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

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

Authorship Contributions: Concept – BEY, AEKG, IIC; Design – BEY, AEKG, IIC; Supervision – HAG, EA; Fundings – BE, EA, HAG; Materials – BE, AEKG, EA; Data collection and/or processing – BE, AEKG, HAG; Analysis and/or interpretation – BE, IIC, HAG; Literature review – BE, AEKG, EA; Writing – BE, AEKG, IIC; Critical review – BE, AEKG, HAG.

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