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RESEARCH

The Effect of Secondary Prophylaxis Adherence on Rheumatic Heart Disease and Determinants of Poor Adherence in Children: A 10-Year Retrospective Cohort Study

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Abstract

Rheumatic heart disease (RHD) remains the leading cause of acquired cardiovascular morbidity and mortality in children. Since secondary prophylaxis is the cornerstone of the management of acute rheumatic fever (ARF) and RHD, this study aimed to assess the impact of prophylaxis adherence on disease recurrence and cardiac outcomes and to identify causes of non-adherence with prophylaxis. We retrospectively reviewed 137 ARF cases diagnosed before the age of 18 years, with a minimum follow-up duration of ≥ 6 months. Diagnosis was based on the Revised Jones criteria. Clinical and echocardiographic evaluations were conducted to assess RHD, and prophylaxis adherence was evaluated through qualitative interviews. The cohort (49% female, mean age 13.97 ± 3.69 years) had a 43.8% rate of cardiac involvement at diagnosis, decreasing to 40.9% at last follow-up, with 38% developing RHD. RHD development was significantly associated with initial carditis presence and worse severity ($p = 0.001$; $p = 0.046$). Adherence to secondary prophylaxis was observed in 88.3% ($n = 121$). Low socioeconomic status, milder valvulitis at diagnosis, and longer follow-up duration were associated with non-adherence ($p = 0.008$; 0.041; 0.001). Adherent patients showed significant reductions in both the number of affected valves ($p = 0.001$) and severity of valvular regurgitation ($p = 0.003$). Recurrence was more frequent among non-adherent patients ($p = 0.005$). Non-adherence to secondary prophylaxis remains a major barrier in ARF/RHD control, as it correlates with more severe valvular involvement and recurrence. Identifying factors influencing adherence may guide future strategies to improve both prophylaxis adherence and long-term outcomes.

Keywords Acute rheumatic fever · Secondary prophylaxis · Rheumatic heart disease · Treatment adherence

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AR	Aortic regurgitation
ARF	Acute rheumatic fever
ASO	Anti-streptolysin O

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CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
GAS	Group A Streptococcus
MR	Mitral regurgitation
OECD	Organization for Economic Co-operation and Development
RHD	Rheumatic heart disease
WHF	World Heart Federation

Introduction

Acute rheumatic fever (ARF) is a diffuse, non-suppurative systemic inflammatory disease triggered by an autoimmune response, typically 2 weeks after group A beta-hemolytic streptococcal tonsillopharyngitis, and it primarily affects the heart, joints, brain, skin, and subcutaneous tissue. While ARF incidence has declined in Europe and North America over recent decades, it remains a major cause of cardiovascular morbidity and mortality among socioeconomically disadvantaged populations, especially in developing countries [1, 2]. Rheumatic heart disease (RHD), a chronic complication of ARF, results from heart valve damage due to either a single severe or more often, recurrent episodes of ARF. According to IHME Global Burden of Disease, RHD affected an estimated 55 million people globally in 2021; this represents a 1.7-fold increase in prevalence since 1990 [3, 4]. The age-standardized death rate was 4.5 per 100,000, corresponding to an estimated 360,000 deaths [3]. In Turkey, the estimated ARF incidence is 8.84 per 100,000, with regional variation supporting its classification as a moderate-risk country [5]. Recurrent ARF can both initiate and exacerbate RHD. Secondary prevention, involving continuous antibiotic chemoprophylaxis to prevent recurrent group A Streptococcus (GAS) infections, remains the cornerstone of ARF/RHD management [6].

However, data evaluating adherence to secondary prophylaxis and its impact on ARF outcomes in large single-center cohorts are limited. The primary aim of this study was to assess the impact of prophylaxis adherence on ARF recurrence and cardiac outcomes. Additionally, we aimed to identify factors contributing to poor adherence to guide preventive strategies.

Methods

This single-center cohort study included 137 ARF patients diagnosed at the Pediatric Cardiology and Rheumatology Departments of Istanbul University-Cerrahpasa Medical Faculty between October 2011 and June 2021.

Patient Selection

Patients over 18 years at the time of diagnosis, with follow-up shorter than 6 months, or lacking informed consent were excluded. All included cases met the applicable "Modified Jones Criteria" at diagnosis. Although the study included patients diagnosed before the age of 18 years, follow-up in a few cases was briefly continued beyond 18 years—up to ages 21–23—according to the national guideline recommendation to maintain prophylaxis until age 21 or 5 years after the last episode, whichever is longer.

Diagnostic Criteria for Acute Rheumatic Fever

Patients were diagnosed using the "1992 Modified Jones Criteria" [7] by experienced faculty from Pediatric Cardiology and Rheumatology. Those diagnosed in 2015 or later were re-evaluated according to both the 1992 and the updated "2015 Modified Jones Criteria" by the *American Heart Association (AHA)* [1] with final diagnoses based on the 2015 guidelines. All patients were assessed according to both sets of criteria [1, 7], and pre-2015 cases were retrospectively re-evaluated using the 2015 criteria.

Data Collection

Clinical and Laboratory Findings

Data on demographics, symptoms, laboratory results (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-streptolysin O (ASO), throat culture), physical examination findings, and echocardiographic/electrocardiographic results at diagnosis, as well as ARF history, treatment and prophylaxis modalities, and recurrences, were collected. Cardiac outcomes were assessed during follow-up through physical examinations and echocardiographic evaluations.

Echocardiographic Evaluation

Echocardiograms were performed using the Philips iE33 device (X5-1, S8-3 probes). Valve anatomy and the presence/severity of valvular regurgitation were assessed. Left heart dimensions, function, fractional shortening, and ejection fraction were measured. Severity of valvular involvement was re-evaluated using qualitative ("eyeballing" of the color flow regurgitation jet) and quantitative methods, including vena contracta width, pulmonary vein flow for mitral regurgitation (MR), and regurgitant jet-to-left ventricular outflow tract diameter ratio for aortic regurgitation (AR) [8–10], by a blinded expert pediatric cardiologist

(F.O). Initial echocardiographic findings were also graded as mild, moderate, or severe according to New Zealand ARF guidelines [10].

Diagnostic Criteria for Rheumatic Heart Disease

RHD was diagnosed according to the 2012 "*World Heart Federation (WHF)* Rheumatic Heart Disease Diagnostic Echocardiographic Criteria" for individuals ≤ 20 years [11]. Mitral valve findings included anterior leaflet thickening ≥ 3 mm (age-specific), chordal thickening, restricted or excessive leaflet motion during systole. Aortic valve findings included irregular or focal thickening, coaptation defect, restricted motion, or prolapsesentence 'RHD was diagnosed according to...'. Please check and

Pathological MR required: Seen in ≥ 2 views, jet length ≥ 2 cm in ≥ 1 view, peak velocity > 3 m/s, and pansystolic jet in ≥ 1 envelope. For AR: Seen in ≥ 2 views, jet length ≥ 1 cm, peak velocity > 3 m/s, and pandiastolic jet in ≥ 1 envelope. Archived echocardiograms were re-evaluated, and RHD diagnoses reviewed per the updated 2023 *WHF* guidelines [12].

Criteria for Acute Rheumatic Fever Recurrences

Recurrence of ARF was defined according to the revised Jones criteria, in patients with a prior history of ARF or established RHD and documented group A streptococcal infection [1, 7].

Secondary Prophylaxis Program

All patients with confirmed ARF (including isolated Sydenham chorea) or RHD were prescribed continuous benzathine penicillin G. Prophylaxis was planned for 10 years post-ARF or until age 40 in those with residual valve disease, and for at least 10 years or until age 21 in those without. In general, prophylaxis continued until age 21 or 5 years after the last episode, whichever was longer [6, 13]. Decisions on discontinuation or reinstatement were individualized, considering risk–benefit profiles and local epidemiology. Given Turkey's moderate-risk status, a 3-weekly benzathine penicillin G regimen was standard practice.

Criteria for Prophylaxis Adherence

Adherence was assessed by recording yes/no responses to number of prophylaxis doses in the last 6 and 12 months, any discontinuation before the *AHA*-recommended schedule (2009) [13], compliance with 21-day dosing, and any missed doses.

According to the *World Health Organization*, adherence is "the extent to which a person's behavior—taking medication, following a diet, and/or making lifestyle changes—corresponds with agreed recommendations from a healthcare provider" [14]. A qualitative interview was developed based on prior literature [15–19].

Non-adherence was defined as early discontinuation of prophylaxis, receiving < 80% of scheduled doses in the past year, or missing all benzathine penicillin doses in the past 6 months. Adherence data were obtained through structured interviews with parents of all patients, supplemented by direct patient interviews in those aged ≥ 12 years when feasible. Qualitative interviews assessed variables including gender, current age, age at diagnosis, follow-up duration and frequency, socioeconomic status, family history, hospitalization history, healthcare access, valvular severity, disease awareness, and the presence/number of recurrences. Socioeconomic status was determined by urban/rural residence, parental education, number of dependents, and household income, and categorized as low, moderate, or high.

Ethical Approval

The study was approved by the Istanbul University-Cerrahpasa Clinical Research Ethics Committee (November 14, 2020/145346) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the parents/legal guardians of all patients, and additionally from patients aged ≥ 12 years, in accordance with the requirements of our institutional ethics committee.

Statistical Analysis

Data were analyzed using SPSS v20.0. Normality of continuous variables was assessed via the Shapiro–Wilk test. Results are presented as number (percentage) for categorical variables, mean (standard deviation) for normally distributed data, and median (minimum–maximum) for skewed data. Categorical associations were analyzed using Chi-square, Fisher's exact, or linear-by-linear tests. Categorical variables with more than two groups (e.g., improvement, no change, worsening) were analyzed using the Fisher–Freeman–Halton test, while Pearson Chi-square test was applied to binary comparisons. Importantly, statistical significance was interpreted in conjunction with clinical relevance, since not all statistically significant results necessarily indicate clinically meaningful differences. For independent groups, Mann–Whitney *U* or Student's *t* tests were used based on distribution; Wilcoxon Signed Ranks for paired nonparametric data. Categorical paired comparisons were assessed using McNemar's test. A $p\ value < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 137 ARF patients ($n=67$, 49% female) were included, with a mean age of 13.97 ± 3.69 years. The mean age at diagnosis was 9.47 ± 2.86 years, and mean follow-up was 4.83 ± 2.79 years. Of these, 109 (79.6%) were diagnosed according to the 1992 Modified Jones Criteria and 28 (20.4%) using the 2015 update. At presentation, arthritis was noted in 70% ($n=96$), carditis in 43.8% ($n=60$), erythema marginatum in 6.6% ($n=9$), chorea in 4.4% ($n=6$), and no subcutaneous nodules were observed. Demographic and clinical characteristics of patients are presented in Table 1.

Heart Involvement and Rheumatic Heart Disease Findings

At diagnosis, 43.8% ($n=60$) had carditis, which decreased to 40.9% ($n=56$) at last follow-up. Isolated MR was the most frequent lesion (48.3%), followed by MR + AR (43.3%) and isolated AR (5%). Among those with regurgitation, mild MR and AR were most common (72% and 87%, respectively), while moderate regurgitation was less frequent (28% MR;

Table 1 Demographic and clinical characteristics

Demographic characteristics		
Gender (*n*, %)	Female	67 (49)
	Male	70 (51)
Age	*Mean ± SD*	13.97 ± 3.69
Age at diagnosis	*Mean ± SD*	9.47 ± 2.86
Follow-up duration	*Mean ± SD*	4.83 ± 2.79
Follow-up frequency (*n*, %)	< 6 months	4 (2.9)
	Every 6 months	56 (40.9)
	Once a year	75 (54.7)
	Every 2 years	2 (1.5)
Socioeconomical status (*n*, %)	Low	7 (5.1)
	Moderate	35 (25.5)
	Moderate-high	24 (17.5)
	High	71 (51.8)
Family history of ARF (*n*, %)	Yes	111 (81.0)
	No	26 (29.0)
Clinical characteristics		
Major criteria		
•Polyarthralgia (*n*, %)		21 (15.3)
•Monoarthritis (*n*, %)		18 (13.1)
Polyarthritis (*n*, %)		96 (70.1)
Carditis (*n*, %)		60 (43.8)
Erythema marginatum (*n*, %)		9 (6.6)
Chorea (*n*, %)		6 (4.4)
Subcutaneous nodule (*n*, %)		0 (0.0)
Minor criteria		
CRP	*Median (min–max)*	6.2 (0–170)
ESR	*Median (min–max)*	69 (9–149)
Prolonged PR interval (*n*, %)		10 (7.3)
Fever (*n*, %)		94 (68.6)
Supporting criteria		
Positive ASO (> 150 IU/ml) (*n*, %)		134 (97.8)
ASO	*Median (min–max)*	650 (112–5350)
Positive throat culture (*n*, %)		13 (9.5)

Data are presented as mean ± standard deviation (SD) for normally distributed variables and as median (minimum–maximum) for non-normally distributed variables; categorical variables are presented as *n* (%)

•These criteria have been accepted as a major criterion according to the 2015 Revised Jones Criteria

ARF acute rheumatic fever, *ASO* anti-streptolysin O, *CRP* C-reactive protein

Table 2 Valvular involvement at diagnosis and follow-up

	Diagnosis *n* (%)	Follow-up *n* (%)
Affected valve		
Mitral valve	29 (48.3)	37 (66.1)
Aortic valve	3 (5.0)	6 (10.7)
Mitral + aortic valves	26 (43.3)	13 (23.2)
Mitral + aortic + tricuspid valves	2 (1.5)	0 (0.0)
The severity of mitral valve involvement		
Very mild	8 (14.0)	20 (40.0)
Mild	33 (58.0)	22 (44.0)
Mild-moderate	6 (10.5)	3 (6.0)
Moderate	10 (17.5)	4 (8.0)
Severe	0 (0.0)	1 (2.0)
The severity of aortic valve involvement		
Very mild	6 (19.4)	7 (36.8)
Mild	21 (67.7)	8 (42.1)
Mild-moderate	2 (6.5)	3 (15.8)
Moderate	2 (6.5)	0 (0.0)
Severe	0 (0.0)	1 (5.3)
The severity of tricuspid valve involvement		
Very mild	1 (50.0)	0 (0.0)
Mild	1 (50.0)	0 (0.0)

Countable data presented as number (percent). Severity of valvulitis was classified as very mild, mild, moderate, or severe according to New Zealand ARF guidelines

Table 3 Valvular involvement at diagnosis and rheumatic heart disease

	RHD		*p* value
	No *n* (%)	Yes *n* (%)	
Valvular involvement (at diagnosis)			
No	68 (81.9)	7 (13.5)	[a]**0.001****
Yes	15 (18.1)	45 (86.5)	
Severity of valvulitis (at diagnosis)			
Very mild	2 (13.3)	4 (8.9)	[d]**0.046***
Mild	12 (80.0)	24 (53.3)	
Moderate	1 (6.7)	17 (37.8)	

Pearson Chi-square and Fisher–Freeman–Halton tests are used for nominal categories. Countable data presented as number (percent). Significant values are written in bold. The threshold for statistical significance was set at p value < 0.05. Severity of valvulitis was classified as very mild, mild, moderate, or severe according to New Zealand ARF guidelines, based on qualitative ("eyeballing" of the color flow regurgitation jet) and quantitative echocardiographic measures (vena contracta width, pulmonary vein flow for MR, regurgitant jet-to-LVOT diameter ratio for AR)

RHD rheumatic heart disease

$^{**}p < 0.01$, $^{*}p < 0.05$

[a]Pearson Chi-square test

[d]Fisher–Freeman–Halton test

13% AR) (Table 2). No valvular stenosis was observed. Valvular findings improved in 52.9%, worsened in 17.6%, and remained unchanged in 29.4%. RHD was present in 38% ($n = 52$), and the updated 2023 WHF criteria did not alter prevalence. RHD development was positively associated with the presence of valvular involvement and with greater severity at onset ($p = 0.001; 0.046$) (Table 3).

Adherence to Secondary Prophylaxis

Secondary prophylaxis was initiated in all patients ($n = 137$), with adherence observed in 88.3% ($n = 121$). Supplementary Information-1 details adherence findings. Secondary prophylaxis adherence was significantly lower in patients who experienced disease recurrence compared to those without recurrence ($p = 0.005$). Adherence was not significantly associated with age, gender, age at diagnosis, follow-up frequency, hospitalization history, family history of ARF, or healthcare access ($p > 0.05$). Poor socioeconomic status, lower awareness of disease severity, and more severe valvular regurgitation at diagnosis were each significantly associated with reduced prophylaxis adherence ($p = 0.008$, $p = 0.001$, and $p = 0.041$, respectively). Adherence decreased with longer follow-up duration, indicating a negative time-dependent association between follow-up length and compliance with secondary prophylaxis ($p = 0.001$) (Tables 4, 5).

Disease Recurrence

ARF recurrence occurred in 22 patients (16%). Among them, 68.2% ($n = 15$) were adherent to prophylaxis, while 31.8% ($n = 7$) were non-adherent. Recurrence was significantly more common among non-adherent patients ($p = 0.005$) (Tables5). Among patients classified as adherent, 15 developed recurrence; these individuals reported occasional missed or delayed doses (e.g., beyond the 21-day interval). However, this difference compared to adherent patients without recurrence was not statistically significant. Severe mitral and aortic regurgitation developed in patients with recurrence and non-adherence.

Outcomes of Valvular Involvement According to Secondary Prophylaxis Adherence

Among prophylaxis-adherent patients, MR improved in 22.7%, remained stable in 69.7%, and worsened in 7.6%; AR improved in 13.4%, remained stable in 84%, and worsened in 2.5%. Worsening was observed in patients with low adherence and recurrent ARF. Adherent patients showed a significant reduction in the number of affected valves ($p = 0.001$),

Table 4 Baseline characteristics and adherence-related variables

	Prophylaxis adherence		
	No ($n=16$)	Yes ($n=121$)	p value
Gender			
Female	6 (9.0)	61 (91.0)	[a]0.332
Male	10 (14.3)	60 (85.7)	
Age			
Mean ± SD	14.55 ± 3.58	13.90 ± 3.71	[b]0.509
Median (min–max)	13.5 (8.8–22)	13.7 (4.8–23.9)	
Age at diagnosis			
Mean ± SD	10.46 ± 2.58	9.34 ± 2.88	[b]0.141
Median (min–max)	9.9 (6.3–16.7)	9.3 (2.6–16.7)	
Follow-up duration			
Mean ± SD	4.10 ± 1.88	4.93 ± 2.88	[c]0.339
Median (min–max)	4 (1.4–8.3)	4.5 (0.6–17.6)	
Follow-up frequency			
< 6 months	0 (0.0)	4 (100.0)	[d]0.809
Every 6 months	8 (14.3)	48 (85.7)	
Once a year	8 (10.7)	67 (89.3)	
Every 2 years	0 (0.0)	2 (100.0)	
Yes	11 (33.3)	22 (66.7)	
Socioeconomic status			
Poor	4 (57.1)	3 (42.9)	[d]**0.008****
Moderate	5 (14.3)	30 (85.7)	
Moderate-good	1 (4.2)	23 (95.8)	
Good	6 (8.5)	65 (91.5)	
Family history			
No	13 (11.7)	98 (88.3)	[e]1.000
Yes	3 (11.5)	23 (88.5)	
Hospitalization			
No	7 (8.3)	77 (91.7)	[a]0.125
Yes	9 (17.0)	44 (83.0)	
Access to healthcare			
No	1 (100.0)	0 (0.0)	[c]0.117
Yes	15 (11.0)	121 (89.0)	
Severity of valvular regurgitation (at diagnosis)			
Very mild	1 (10.0)	5 (10.0)	[d]**0.041***
Mild	9 (90.0)	27 (54.0)	
Moderate	0 (0.0)	18 (36.0)	
Understanding of disease severity			
No	7 (70.0)	3 (30.0)	[c]**0.001****
Yes	9 (7.1)	118 (92.9)	

Data are presented as number (percent) for categorical variables and as mean ± SD or median (min–max) for continuous variables, as appropriate. Statistical significance was set at $p<0.05$. Significant comparisons are shown in bold. Comparisons were performed using Pearson's chi-square, Fisher's exact or Fisher–Freeman–Halton test for categorical variables and t test or Mann–Whitney U test for continuous variables. "Hospitalization" refers to admission for ARF/RHD-related events at the time of initial diagnosis

*$p<0.05$, **$p<0.01$

[a]Pearson Chi-square test

[b]Student t test

[c]Mann–Whitney U test

[d]Fisher–Freeman–Halton test

[e]Fisher's exact test

Table 5 Adherence-related clinical outcomes during follow-up

	Prophylaxis adherence		
	No ($n=16$)	Yes ($n=121$)	p value
Decrease in adherence with longer follow-up			
No	5 (4.8)	99 (95.2)	[a]**0.001****
Yes	11 (33.3)	22 (66.7)	
Disease recurrence			
No	9 (7.8)	106 (92.2)	[a]**0.005****
Yes	7 (31.8)	15 (68.2)	
Number of disease recurrences			
Once	3 (37.5)	5 (62.5)	[b]0.156
≥ 2 times	3 (60.0)	2 (40.0)	
Occasionally	1 (11.1)	8 (88.9)	

Data are presented as number (percent) for categorical variables Statistical significance was set at $p<0.05$. Significant comparisons are shown in bold. Comparisons were performed using Fisher's exact or Fisher–Freeman–Halton test for categorical variables. "Decrease in adherence with longer follow-up" was defined as a reduction in the proportion of scheduled prophylaxis doses received over the observation period

**$p<0.01$

[a]Pearson Chi-square test

[b]Fisher–Freeman–Halton test

[a]Fisher's exact test

severity of regurgitation ($p=0.003$), and frequency of aortic valve involvement ($p=0.002$), indicating better cardiac outcomes (Table 6).

Discussion

Our findings show a correlation between strict adherence to secondary prophylaxis and lower rates of RHD—which remains a significant cause of cardiac morbidity—and highlight its potential role in improving cardiac outcomes. The study also identifies the underlying reasons for non-adherence to prophylactic treatment.

Although ARF and its sequela RHD contribute substantially to morbidity and mortality in developing countries, they remain underrecognized global health issues [20]. The REMEDY registry in low- and middle-income countries reported that 63.9% of RHD patients had advanced disease and complications at diagnosis [21]. The clinical profile of ARF in these regions closely mirrors that of high-income countries, with carditis and arthritis being the most frequent major manifestations during initial episodes, followed by

Table 6 Changes in valvular involvement according to prophylaxis adherence

	Prophylaxis adherence		*p*
	No	Yes	
	n (%)	*n* (%)	
Heart involvement (at diagnosis)			
No	6 (37.5)	69 (58.0)	[a]0.122
Yes	10 (62.5)	50 (42.0)	
Heart involvement (follow-up)			
No	7 (43.8)	74 (61.2)	[a]0.183
Yes	9 (56.3)	47 (38.8)	
p	[f]**0.564**	[f]**0.467**	
Course of heart involvement			
Improvement	2 (12.5)	10 (8.4)	[d]0.728
No change	13 (81.3)	102 (85.7)	
Worsening	1 (6.3)	7 (5.9)	
Severity of valvular regurgitation (at diagnosis)			
Very mild	1 (10.0)	5 (10.0)	[d]**0.041***
Mild	9 (90.0)	27 (54.0)	
Moderate	0 (0.0)	18 (36.0)	
Severity of valvular regurgitation (follow-up)			
Very mild	4 (44.4)	20 (42.5)	[d]1.000
Mild	4 (44.4)	19 (40.4)	
Moderate	1 (11.1)	6 (12.8)	
Severe	0 (0.0)	2 (4.3)	
p	[f]**0.564**	[f]**0.003****	
Change in the severity of valvular regurgitation			
Improvement	4 (36.4)	31 (54.4)	[d]0.458
No change	5 (45.5)	16 (28.1)	
Worsening	2 (18.2)	10 (17.5)	
Affected valves (at diagnosis)			
Aortic	0 (0.0)	3 (6.0)	[d]0.894
Mitral	6 (60.0)	23 (46.0)	
Mitral + aortic	4 (40.0)	22 (44.0)	
Mitral + aortic + tricuspid	0 (0.0)	2 (4.0)	
Number of affected valves			
Mean ± *SD*	1.40 ± 0.52	1.52 ± 0.58	
Median (min–max)	1 (1–2)	1 (1–3)	
Affected valves (follow-up)			
Aortic	0 (0.0)	6 (12.8)	[d]0.539
Mitral	6 (66.7)	31 (66.0)	
Mitral + aortic	3 (33.3)	10 (21.3)	
Number of affected valves			
Mean ± *SD*	1.33 ± 0.50	1.21 ± 0.41	
Median (min–max)	1 (1–2)	1 (1–2)	
p	[f]**1.000**	[f]**0.001****	
Change in the number of affected valves			
Regression	2 (18.2)	22 (38.6)	[d]0.417
No change	8 (72.7)	28 (49.1)	
Progression	1 (9.1)	7 (12.3)	

Categorical data are presented as number (percentage); continuous normally distributed data are presented as mean (standard deviation), and skewed data are presented as median (minimum–maximum). Significant values are written in bold. Wilcoxon Signed Ranks Test was used for skewed data; Pearson Chi-square and Fisher–Freeman–Halton tests were used for categorical variables. A p value < 0.05 was considered statistically significant. Fisher–Freeman–Halton exact test was applied due to small cell counts. P values represent overall distribution differences but may not fully reflect clinical significance given the limited sample size, especially in the 'worsening' category

*$p < 0.05$, **$p < 0.01$

[a]Pearson Chi-square test

[d]Fisher–Freeman–Halton test

[f]Wilcoxon signed ranks test

chorea, subcutaneous nodules, and erythema marginatum [2, 22–24]. Our cohort showed similar distribution, with a slightly lower rate of carditis, likely due to the exclusion of subclinical carditis as a major criterion prior to 2015. In our study, 79.6% were diagnosed using the 1992 Modified Jones Criteria, while all patients fulfilled the 2015 version. Retrospective re-evaluation showed that 20.4% would not have been diagnosed under the 1992 criteria, consistent with findings from Guler et al. (18%) and Licciardi et al. (20.7%) [25, 26]. The inclusion of monoarthritis and subclinical carditis in the updated criteria likely enhances diagnostic sensitivity, particularly in high-risk populations [1].

Approximately, 50–70% of patients with carditis during the initial ARF episode recover without permanent damage, while regression of cardiac involvement after 10 years occurs in 10–25%. Meira et al. reported that 59.4% of patients with mild/moderate carditis showed regression, whereas no improvement was noted in those with severe involvement [27]. Gunes et al. found that 82% of patients with clinical carditis had persistent valvular lesions at 1 year, with a decrease in regurgitation severity in 39% [28]. Other small cohort studies reported remission in 32–46% and regression of definite RHD in 30–45% of children [29–32], aligning with our RHD rate of 38%. Variability in RHD rates across studies likely reflects small sample sizes and the single-center, tertiary care setting, limiting generalizability. We expect greater regression with longer follow-up. In line with prior studies [19, 33, 34], our findings confirm that the presence and severity of cardiac involvement at diagnosis are key predictors of RHD development, highlighting the need for early detection of carditis.

Secondary prophylaxis remains central to ARF/RHD management [6]. While primary prevention strategies aimed at early risk reduction have been emphasized [35], recurrence is consistently higher in patients with poor adherence [17, 28, 36, 37], aligning with our findings showing significantly fewer recurrences in adherent patients. Notably, 15 patients classified as adherent still experienced recurrence, which on closer review reflected occasional missed or delayed doses, underscoring the importance of consistent

administration. The absence of statistical significance within the adherent subgroup likely reflects small sample size and imperfect capture of "true" adherence, rather than the absence of an effect. Good adherence has been shown to reduce ARF recurrence and RHD progression by up to 71% [38]. In our cohort, adherent patients had fewer affected valves, milder valvular regurgitation, and more marked regression in aortic involvement. Beaton et al. [39] also demonstrated reduced disease progression in adherent individuals [39]. In a large cohort with prolonged follow-up, no recurrences or progression occurred in patients receiving regular prophylaxis, and 69.8% and 48.7% showed regression in mitral and aortic lesions, respectively [40]. A 2024 meta-analysis confirmed that intramuscular antibiotics significantly reduce ARF recurrence, particularly in early or mild RHD [41]. Although a recent study found no increased RHD risk with poor adherence in developed countries [19], modifications to prophylaxis schedules should await confirmation in broader prospective trials.

Poor adherence to secondary prophylaxis remains a key challenge in ARF/RHD control. Global non-adherence rates range from 10 to 65.7% [37], while our study showed a notably higher adherence rate (88.3%). A recent systematic review also reported adherence rates exceeding 90% [18]. High accessibility to healthcare (99.2%) and patient understanding of disease severity (92.7%) may explain our findings. These factors likely facilitate timely prophylaxis administration and sustained engagement with healthcare providers. Although Turkey has fewer physicians per 100,000 people (239 vs. Organization for Economic Co-operation and Development (OECD) average of 377), it reports higher physician consultation rates (11.4 vs. OECD average of 6.4), with over half occurring in secondary/tertiary centers. Given that administration of the injection requires presentation to a healthcare facility, these indicators highlight the high level of accessibility and utilization of healthcare services across the country, despite a lower physician-to-population ratio. Furthermore, despite seasonal or rural barriers, general healthcare access remains adequate. In our study, lower adherence was significantly more frequent among patients with low socioeconomic status, longer follow-up duration, and milder valve involvement at diagnosis. Conversely, extended hospital stays and lifestyle limitations (e.g., reduced quality of life due to extended restrictions from school and daily activities) may improve understanding of disease severity and of potential complications and therefore result in higher adherence. The finding that poor socioeconomic status was significantly associated with lower adherence underscores the need for targeted social and healthcare support to reduce disparities in secondary prophylaxis uptake. Interestingly, patients with inadequate understanding of their disease severity were significantly less adherent to prophylaxis, suggesting that structured patient and family education could be an effective strategy to improve compliance. Moreover, the significant decline in adherence with longer follow-up duration emphasizes the importance of sustained patient engagement and regular counseling throughout the follow-up period. Literature, including a systematic review, indicates that factors such as symptomatic ARF, moderate/severe RHD, adequate healthcare access, strong patient–provider relationships, large households, shorter follow-up, younger age, and female sex are associated with better adherence, whereas rural residence, limited healthcare access, poor patient–provider relationships, lack of family support, adolescence, long follow-up, and weak health system engagement predict non-adherence [15–17, 37, 43]. A recent meta-analysis also cited financial barriers, distance, fear of injections, and poor counseling/poor disease knowledge as major contributors to low adherence, with a pooled adherence rate of 58.5% [44]. Recent evidence supports the role of community-based interventions in improving adherence to secondary prophylaxis. The CAMPS Trial in Uganda showed that integrating community health worker support into routine care significantly increased benzathine penicillin adherence [45]. Additional strategies include reminder systems, school-based delivery, and mobile messaging. In our context, high healthcare accessibility (99.2%) and patient awareness of disease severity (92.7%) suggest that strengthening patient education through clinician–patient interactions, public health campaigns, and educational materials, as well as ensuring regular follow-up of prophylaxis-requiring cases at the primary care level, may help maintain and further improve these adherence rates.

Limitations

This study has several limitations. A clear distinction between clinical and subclinical carditis could not be made, particularly in pre-2015 diagnoses, limiting evaluation of cardiac prognosis in this group. As all patients received secondary prophylaxis and the study lacked a randomized controlled design, causal inferences on prophylaxis outcomes are limited. Prophylaxis adherence was assessed through self-reported interviews, which may introduce recall bias and lead to over- or underestimation of adherence. This possibility is further supported by the discrepancy observed between the "number of administered doses" and the "number of missed doses" reported in the last year. Although all patients underwent follow-up echocardiography, baseline data were missing in two cases, and overlap of mitral and aortic involvement led to dual representation in both categories. This should be regarded as a limitation of data completeness and classification rather than unequal follow-up. Finally, the use of both 1992 and 2015 Jones criteria may cause diagnostic

inconsistency; however, applying the 2015 revision allowed identification of cases that would not have met earlier criteria, underscoring the importance of updated diagnostic standards.

Conclusion

Although direct efficacy was not demonstrated, our findings support strict adherence to secondary prophylaxis in all patients. This cohort study underscores its pivotal role in preventing ARF recurrences and progression to permanent valvular damage, with improved outcomes such as reduced carditis severity and less aortic involvement. Further qualitative research into adherence factors is warranted to guide strategies that optimize prophylaxis implementation and enhance cardiac prognosis.

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Data Availability All data relevant to the study are included in the article. The corresponding author is the guarantor for any additional information or any queries regarding the article and could be reached through any of the contact information given.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki (2013 revision). Approval was granted by the Ethics Committee of Istanbul University-Cerrahpasa (November 14, 2020/145346).201.

Consent to Participate Written informed consent was obtained from the parents, and participants ≥ 12 years included in the study.

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