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Original Article

Evaluation of High Sensitivity C Reactive Protein and Cardiac Biomarkers in Pediatric Patients with Rheumatic Heart Disease

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ABSTRACT

Background: Rheumatic heart disease (RHD) remains a major cause of acquired cardiovascular morbidity among children in developing countries, including India. Persistent inflammation and myocardial injury contribute to progressive valvular damage. High-sensitivity C-reactive protein (hs-CRP) and cardiac biomarkers may serve as indicators of inflammatory activity and cardiac involvement. Elevated hs-CRP has been associated with severity and progression of rheumatic valvular disease, suggesting ongoing inflammatory activity beyond acute rheumatic fever.
Aim: To evaluate serum hs-CRP and cardiac biomarkers in pediatric patients with rheumatic heart disease and determine their association with disease severity.
Materials and Methods: This hospital-based prospective case-control study included 80 children aged 5–18 years. Forty diagnosed pediatric RHD patients constituted the study group and forty age- and sex-matched healthy children served as controls. Clinical examination, echocardiography, hs-CRP estimation, and cardiac biomarkers including Troponin-I, CK-MB, and NT-proBNP were analyzed.
Results: Mean hs-CRP levels were significantly higher among RHD patients compared with controls (3.81±1.92 vs 0.74±0.33 mg/L; $p<0.001$). Troponin-I, CK-MB and NT-proBNP levels were also elevated in cases. hs-CRP demonstrated positive correlation with severity of valvular lesions and left ventricular dysfunction.
Conclusion: Pediatric RHD patients showed significantly increased hs-CRP and cardiac biomarker levels. These biomarkers may assist in assessing inflammatory burden, myocardial involvement, and disease severity.

Keywords: *Rheumatic heart disease, hs-CRP, Troponin-I, CK-MB, NT-proBNP, Pediatrics.*

INTRODUCTION

Rheumatic heart disease (RHD) remains one of the most important causes of acquired cardiovascular morbidity and mortality among children and adolescents in developing nations including India. Despite improvements in healthcare infrastructure, RHD continues to impose a substantial disease burden due to delayed diagnosis, recurrent streptococcal infections, poverty, and inadequate implementation of secondary prophylaxis. [1,2] According to recent global estimates, more than 39 million individuals are affected worldwide, with South Asia contributing significantly to disease prevalence.[3]

RHD is a chronic sequela of acute rheumatic fever (ARF), an autoimmune inflammatory disease triggered by infection with Group A β-hemolytic streptococci. Molecular mimicry between streptococcal antigens and host cardiac tissue leads to persistent inflammatory and immunologic injury involving valvular endocardium and myocardium.[4] Traditionally, disease progression was believed to be associated solely with recurrent rheumatic fever episodes; however, accumulating evidence suggests persistent low-grade inflammation even in chronic stages of disease.[5]

Inflammation plays a pivotal role in valvular fibrosis, calcification, and progressive myocardial dysfunction. Recent histopathological studies have demonstrated continued inflammatory cell infiltration and cytokine activity in rheumatic valves despite eradication of active infection.[6] Persistent inflammatory activity contributes to progressive valvular dysfunction and may influence disease severity.

High sensitivity C-reactive protein (hs-CRP) is an acute-phase reactant synthesized by hepatocytes under the influence of inflammatory cytokines including interleukin-6. Unlike conventional CRP assays, hs-CRP can detect low-grade inflammation and has become an important biomarker in cardiovascular diseases.[7] Elevated hs-CRP concentrations have been associated with endothelial dysfunction, atherosclerosis, and chronic inflammatory cardiac disorders.[8]

Several investigators have demonstrated significantly elevated hs-CRP levels in patients with RHD and suggested that persistent inflammation may continue during the chronic phase of disease. Chandrashekhar et al. observed elevated hs-CRP concentrations among patients with rheumatic valvular lesions and reported significant correlations with severity of disease.[9] Similar observations were made in Indian populations where hs-CRP was found to correlate with progression of valvular pathology.[10]

In addition to inflammation, myocardial involvement plays an important role in determining prognosis in pediatric RHD. Cardiac biomarkers such as Troponin-I, CK-MB, and N-terminal pro-brain natriuretic peptide (NT-proBNP) are widely used indicators of myocardial injury and ventricular stress.[11] Troponin-I serves as a highly specific marker of myocardial injury, whereas CK-MB reflects myocardial tissue damage. NT-proBNP is released in response to ventricular volume overload and myocardial strain.[12]

Recent studies suggest that biomarker-based evaluation can facilitate early detection of subclinical myocardial dysfunction and improve risk stratification.[13] Emerging Indian molecular studies have further identified novel inflammatory biomarkers associated with disease severity and progression in RHD patients.[14]

Because pediatric patients frequently remain asymptomatic until significant valvular damage develops, early identification of inflammatory and cardiac biomarkers may help identify high-risk patients and guide disease monitoring. Therefore, the present study aimed to evaluate hs-CRP and cardiac biomarkers in pediatric patients with rheumatic heart disease and determine their relationship with disease severity.

Aim:
To evaluate high sensitivity C-reactive protein and cardiac biomarkers in pediatric patients with rheumatic heart disease

Objectives:
1. To estimate serum hs-CRP levels in pediatric RHD patients.
2. To evaluate cardiac biomarkers (Troponin-I, CK-MB, NT-proBNP).
3. To compare biomarker levels with healthy controls.
4. To assess correlation with disease severity.

MATERIAL AND METHODS:

Study Design and Study Setting
The present study was designed as a prospective hospital-based case–control observational study conducted in the Department of Pediatrics in collaboration with the Department of Pediatric Cardiology and Department of Biochemistry at a tertiary care teaching hospital in Rajasthan, India. The study was carried out over a period of 18 months after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from parents or legal guardians, and assent was obtained from children whenever applicable according to institutional ethical guidelines.

Study Population
The study population consisted of pediatric patients diagnosed with rheumatic heart disease (RHD) attending pediatric outpatient clinics, inpatient wards, and pediatric cardiology services. Age- and sex-matched apparently healthy children presenting for routine health evaluations or vaccination services were included as controls.

The diagnosis of rheumatic heart disease was established based on clinical examination and echocardiographic findings according to revised diagnostic recommendations and standard echocardiographic criteria.[1,2]

Sample Size Calculation
The sample size was calculated considering previous studies evaluating inflammatory markers among RHD patients with an expected difference in hs-CRP levels between cases and controls. Assuming a confidence interval of 95%, power of study of 80%, and α error of 5%, the estimated minimum sample size was calculated to be 36 subjects per group. To compensate for possible attrition and incomplete data, a total of 80 children were included.

Total participants:

- Study group (Cases): 40 pediatric RHD patients
- Control group: 40 healthy children

Total sample size = 80 participants

Sampling Technique

A consecutive sampling technique was employed. All eligible pediatric patients diagnosed with RHD and meeting inclusion criteria during the study period were enrolled until the required sample size was achieved.

Inclusion Criteria

Children fulfilling the following criteria were included:

1. Children aged between 5–18 years
2. Confirmed diagnosis of rheumatic heart disease on echocardiography[1]
3. Patients with isolated or mixed rheumatic valvular lesions
4. Clinically stable patients during enrollment
5. Parents willing to provide informed written consent

Exclusion Criteria

Children with any of the following conditions were excluded:

1. Congenital heart diseases
2. Acute rheumatic fever during active inflammatory phase
3. Acute febrile illness or recent infection within previous four weeks
4. Chronic kidney disease
5. Chronic liver disease
6. Autoimmune disorders
7. Malignancy
8. Recent cardiac surgery
9. Severe malnutrition
10. Patients receiving immunosuppressive drugs

Study Procedure

After enrollment, each participant underwent detailed clinical evaluation according to a predesigned structured case record form.

Data collected included:

A. Demographic variables

- Age
- Gender
- Weight
- Height
- Body mass index
- Socioeconomic status
- Residence (rural/urban)

B. Clinical History

Detailed history was recorded regarding:

- Duration of symptoms
- Breathlessness
- Fatigability
- Palpitations
- Joint pain
- Fever
- Previous acute rheumatic fever episodes
- Previous hospitalization
- History of penicillin prophylaxis
- Drug treatment history
- Family history of cardiovascular disease

C. Clinical Examination

Comprehensive physical examination was conducted including:

General examination:

- Pulse rate

- Respiratory rate
- Temperature
- Blood pressure
- Oxygen saturation
- Anthropometric measurements

Systemic examination:
- Cardiovascular examination
- Presence of murmurs
- Signs of heart failure
- Functional classification according to the New York Heart Association (NYHA)

D. Echocardiographic Assessment
All study subjects underwent two-dimensional echocardiography with Doppler examination using a standardized pediatric echocardiography machine performed by an experienced pediatric cardiologist blinded to laboratory findings.

Parameters recorded included:
- Mitral regurgitation
- Mitral stenosis
- Aortic regurgitation
- Aortic stenosis
- Mixed valvular lesions
- Left ventricular ejection fraction
- Left ventricular dimensions
- Left atrial size
- Pulmonary artery pressure

Severity of valvular lesions was categorized into mild, moderate, and severe according to standard echocardiographic guidelines.[2]

E. Blood Sample Collection
After overnight fasting, approximately 5 mL of venous blood was collected from all participants under aseptic precautions. Blood samples were divided into:
- EDTA tubes
- Plain tubes

Samples were centrifuged at 3000 rpm for 10 minutes, and serum was separated immediately. Aliquots were stored at −80°C until biochemical analysis.

F. Laboratory Investigations
Routine investigations performed included:
- Complete blood count
- Erythrocyte sedimentation rate (ESR)
- Antistreptolysin O (ASO) titer
- Renal function tests
- Liver function tests
- Chest radiography
- Electrocardiography

G. Estimation of High-Sensitivity C-Reactive Protein (hs-CRP)
Serum hs-CRP levels were estimated using high-sensitivity immunoturbidimetric assay on an automated biochemical analyzer.
Principle:

The assay is based on antigen-antibody reaction between CRP present in serum and specific anti-CRP antibodies. Formation of immune complexes results in turbidity proportional to concentration measured photometrically.[3] Results were expressed in mg/L**.**

H. Measurement of Cardiac Biomarkers
Troponin-I estimation: Troponin-I levels were measured using chemiluminescent microparticle immunoassay (CMIA). Results expressed in ng/mL**.**

CK-MB estimation: Creatine kinase-MB levels were estimated by kinetic enzyme immunoassay. Results expressed in U/L.

NT-proBNP estimation: Serum NT-proBNP concentrations were analyzed using sandwich enzyme-linked immunosorbent assay (ELISA). Results expressed in pg/mL.

Internal quality controls and calibration standards were performed before each assay batch.

Outcome Measures

Primary outcome measures:

- Mean serum hs-CRP levels in RHD patients and controls
- Cardiac biomarker levels (Troponin-I, CK-MB, NT-proBNP)

Secondary outcome measures:

- Correlation of biomarkers with severity of valvular lesions
- Association with ventricular dysfunction
- Correlation with echocardiographic parameters

Statistical Analysis:

Data were entered in Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) software version 26.0. Continuous variables were represented as mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. Normality of quantitative variables was assessed using Kolmogorov–Smirnov test. Comparisons between groups were performed using Student's independent t-test , Mann–Whitney U test for nonparametric variables , Chi-square test & Fisher exact test where appropriate .Correlation between hs-CRP and cardiac biomarkers with disease severity was assessed using Pearson correlation coefficient. Multivariate linear regression analysis was performed to determine independent predictors of disease severity. P value <0.05 was considered statistically significant.

RESULTS

A total of 80 participants were included in the study comprising 40 pediatric patients diagnosed with rheumatic heart disease (RHD) and 40 age- and sex-matched healthy controls. Statistical comparisons were performed between both groups to evaluate inflammatory and cardiac biomarker profiles and their relationship with disease severity.

The study and control groups were comparable regarding age, gender distribution, anthropometric measurements, and residential background. No statistically significant differences were observed ($p>0.05$), indicating adequate matching and minimizing demographic confounding factors.(Table1) Breathlessness was the most common presenting symptom observed in 75% of cases, followed by palpitations and fatigability. Nearly half of patients had a history of acute rheumatic fever, and poor compliance with penicillin prophylaxis was common, suggesting possible contribution to disease progression.(Table2)

Mitral regurgitation represented the predominant valvular abnormality followed by aortic regurgitation. Combined valvular involvement was observed in nearly half of patients. Significant proportions also exhibited pulmonary hypertension and ventricular dysfunction, reflecting progressive disease severity.(Table3) Moderate disease severity was observed most frequently among pediatric patients, followed by severe disease. This indicates that a considerable proportion of children presented with advanced disease at diagnosis.(Table4)

ESR, ASO titers, and hs-CRP levels were significantly elevated among RHD patients compared with healthy controls. Increased hs-CRP values support ongoing inflammatory activity in chronic rheumatic heart disease.(Table5) All cardiac biomarkers were significantly elevated among pediatric RHD patients. Raised Troponin-I and CK-MB suggest subclinical myocardial injury, while increased NT-proBNP indicates ventricular stress associated with chronic valvular disease.(Table6)

Increasing biomarker levels were observed with progression of disease severity. Patients with severe RHD demonstrated the highest hs-CRP and cardiac biomarker concentrations, indicating greater inflammatory burden and myocardial stress**.**(Table7) hs-CRP demonstrated significant positive correlations with disease severity, ventricular dysfunction, pulmonary artery pressure, and NT-proBNP levels. This finding suggests that inflammatory activity increases with worsening cardiac involvement.(Table8) hs-CRP and NT-proBNP emerged as strong independent predictors of severe rheumatic heart disease. These biomarkers may have potential utility in risk stratification and prognostic assessment.(Table9)

Table 1: Demographic Characteristics of Study Participants

Variable	Cases (n=40)	Controls (n=40)	P value
Age (years)	11.6 ± 3.2	11.1 ± 2.9	0.54(NS)
Male	22 (55%)	21 (52.5%)	0.82(NS)
Female	18 (45%)	19 (47.5%)	0.82(NS)
Weight (kg)	31.2 ± 8.7	32.4 ± 7.9	0.48(NS)
Height (cm)	136.8 ± 12.4	138.6 ± 10.9	0.57(NS)
BMI (kg/m²)	16.4 ±1.8	16.8 ±1.6	0.31(NS)
Rural residence	26 (65%)	24 (60%)	0.64(NS)
Urban residence	14 (35%)	16 (40%)	0.64(NS)

Table 2: Clinical Characteristics among Pediatric RHD Patients

Clinical Variable	Frequency (n=40)	Percentage
Breathlessness	30	75%
Palpitations	24	60%
Fatigability	22	55%
Chest discomfort	10	25%
Joint pain	15	37.5%
Previous acute rheumatic fever	18	45%
Irregular penicillin prophylaxis	20	50%
Congestive heart failure symptoms	8	20%

Table 3: Distribution of Valvular Lesions on Echocardiography

Echocardiographic Findings	Number	Percentage
Mitral regurgitation	26	65%
Mitral stenosis	10	25%
Aortic regurgitation	14	35%
Aortic stenosis	4	10%
Combined valvular lesions	18	45%
Pulmonary hypertension	12	30%
Left ventricular dysfunction	11	27.5%

Table 4: Severity Distribution of Rheumatic Heart Disease

Disease Severity	Number	Percentage
Mild	11	27.5%
Moderate	17	42.5%
Severe	12	30%

Table 5: Comparison of Inflammatory Markers Between Groups

Inflammatory Marker	Cases	Controls	P value
ESR (mm/hr)	36.8 ±10.5	14.2 ±4.6	<0.001(HS)
ASO titer (IU/mL)	362±84	118±42	<0.001(HS)
hs-CRP (mg/L)	3.81±1.92	0.74±0.33	<0.001(HS)

Table 6: Comparison of Cardiac Biomarkers Between Cases and Controls

Cardiac Biomarker	Cases	Controls	P value
Troponin-I (ng/mL)	0.12±0.04	0.03±0.01	<0.001(HS)
CK-MB (U/L)	38.5±8.7	20.4±4.8	<0.001(HS)

Cardiac Biomarker	Cases	Controls	P value
NT-proBNP (pg/mL)	380±112	98±36	<0.001(HS)

Table 7: Biomarker Levels According to Disease Severity

Biomarker	Mild	Moderate	Severe	P value
hs-CRP (mg/L)	1.82±0.64	3.12±1.03	5.78±1.84	<0.001(HS)
Troponin-I (ng/mL)	0.05±0.02	0.11±0.03	0.18±0.06	<0.001(HS)
CK-MB (U/L)	25.8±5.4	35.6±6.2	48.2±9.3	<0.001(HS)
NT-proBNP (pg/mL)	164±52	328±80	544±106	<0.001(HS)

Table 8: Correlation of hs-CRP with Echocardiographic Parameters

Variable	Correlation coefficient (r)	P value
Disease severity score	0.63	<0.001(HS)
Left ventricular dysfunction	0.48	0.004(HS)
Pulmonary artery pressure	0.42	0.01(S)
NT-proBNP	0.59	<0.001(HS)

Table 9: Multivariate Regression Analysis for Predictors of Severe Disease

Variable	β coefficient	95% CI	P value
hs-CRP	0.52	0.28–0.74	0.001(HS)
NT-proBNP	0.46	0.22–0.69	0.002(HS)
Troponin-I	0.34	0.12–0.58	0.01(S)
CK-MB	0.29	0.09–0.48	0.02(S)

DISCUSSION:

Rheumatic heart disease (RHD) remains a major contributor to cardiovascular morbidity among children in low- and middle-income countries, particularly in South Asia and India. Despite improvements in preventive healthcare strategies, RHD continues to affect children from socioeconomically disadvantaged populations and remains an important cause of chronic valvular heart disease.[1,2] The present study evaluated inflammatory activity using high-sensitivity C-reactive protein (hs-CRP) and assessed myocardial involvement through cardiac biomarkers including Troponin-I, CK-MB, and NT-proBNP among pediatric patients with RHD. The findings demonstrated significantly elevated inflammatory and cardiac biomarkers in cases compared with controls, indicating persistent inflammatory activation and myocardial stress.

In the present study, the mean age of RHD patients was 11.6 ± 3.2 years with slight male predominance (55%). Similar age distributions have been reported in Indian pediatric studies where RHD frequently presents during late childhood and adolescence. Ray et al.[17] and Anbarasan et al.[18] observed that school-age children and adolescents represented the most commonly affected population. This age predisposition may reflect cumulative exposure to recurrent streptococcal infections and delayed disease detection.

Breathlessness (75%), palpitations (60%), and fatigability (55%) were the predominant presenting symptoms in the current study. Similar observations have been reported in previous Indian studies where dyspnea and exercise intolerance were the principal manifestations among pediatric RHD patients.[20] The predominance of breathlessness may be attributed to progressive valvular dysfunction leading to pulmonary venous congestion and ventricular overload.

Mitral regurgitation was the most common echocardiographic lesion (65%), followed by combined valvular involvement (45%). These findings are consistent with previous reports indicating that the mitral valve is most frequently affected in rheumatic heart disease. Marijon et al.[5] reported that mitral regurgitation predominates during early disease stages in children, whereas mitral stenosis and mixed lesions become increasingly common during later stages. Similar observations were reported by Indian community screening studies.[21]

One of the major findings of the present study was significantly elevated hs-CRP levels among pediatric RHD patients compared with healthy controls (3.81±1.92 vs 0.74±0.33 mg/L; $p<0.001$). Elevated hs-CRP suggests persistence of chronic inflammatory activity despite the absence of acute rheumatic fever episodes. These findings support growing evidence that chronic rheumatic valve disease is not merely a static residual lesion but an active inflammatory process.[6]

Our observations are comparable with the findings of Chandrashekhar et al.[9] who demonstrated significantly elevated hs-CRP concentrations in patients with rheumatic valvular disease and proposed ongoing inflammatory mechanisms

contributing to disease progression. Gupta et al.[10] similarly reported elevated hs-CRP concentrations among Indian RHD patients and found significant associations with valvular severity. Alyan et al.[15] observed increased hs-CRP levels among severe mitral valve disease patients and reported positive associations with disease progression.

Persistent inflammatory activity in chronic RHD has been increasingly recognized by histopathological studies. Gomes et al.[6] identified inflammatory infiltrates consisting of macrophages, activated T lymphocytes, and cytokines within rheumatic valve tissue, supporting the hypothesis of ongoing immunologic activation. Such inflammatory responses may accelerate fibrosis, neovascularization, and valvular calcification.

The present study demonstrated significantly elevated ESR and ASO titers among cases. Elevated ASO titers indicate prior exposure to streptococcal infection and support the etiological role of Group A β-hemolytic streptococci. Similar findings have been observed in previous pediatric RHD investigations.[22] Elevated inflammatory markers may represent residual immunologic activity even during clinically quiescent disease stages.

Another important finding of the present study was the significant elevation of Troponin-I and CK-MB levels among RHD patients. Troponin-I is a highly sensitive marker of myocardial injury, whereas CK-MB reflects myocardial tissue damage. Elevation of these biomarkers in the present study suggests possible subclinical myocardial involvement even in the absence of overt myocardial disease.

Comparable findings have been reported in studies evaluating inflammatory cardiac disorders. Saheera et al.[11] described the growing utility of cardiac biomarkers in identifying early myocardial involvement before overt ventricular dysfunction develops. Similar elevations in cardiac biomarkers have also been observed among patients with inflammatory cardiomyopathies and valvular heart diseases.[23]

The current study also observed markedly increased NT-proBNP concentrations among pediatric RHD patients. NT-proBNP is released from ventricular myocardium in response to myocardial stretch and volume overload. Elevated NT-proBNP likely reflects ventricular remodeling secondary to chronic valvular dysfunction.

Our findings are comparable with Januzzi et al.[12] who reported increased natriuretic peptide levels among patients with valvular heart disease and ventricular dysfunction. Chugh et al.[16] similarly demonstrated significant elevation of NT-proBNP in patients with rheumatic valvular lesions and suggested its role in monitoring disease progression.

An important observation in the present study was the progressive increase in hs-CRP, Troponin-I, CK-MB, and NT-proBNP with increasing disease severity. Patients with severe RHD demonstrated the highest biomarker levels compared with mild disease. This suggests that inflammatory burden and myocardial stress increase proportionately with valvular damage.

Similarly, Gupta et al.[10] and Sharma et al.[14] reported significant associations between inflammatory markers and severity of rheumatic valvular lesions. Sharma et al. identified serum inflammatory proteins associated with severe disease and suggested their potential utility in prognostic stratification.

The present study further demonstrated significant positive correlations between hs-CRP and echocardiographic indicators including disease severity score, pulmonary artery pressure, left ventricular dysfunction, and NT-proBNP levels. The positive association between inflammatory activity and ventricular stress suggests that chronic inflammation may contribute not only to valvular injury but also to myocardial remodeling.

Previous investigators have reported similar findings. Ghosh et al.[13] demonstrated correlations between biomarkers and subclinical cardiac dysfunction in pediatric cardiovascular diseases. Persistent inflammation may stimulate cytokine-mediated myocardial fibrosis, endothelial dysfunction, and adverse cardiac remodeling.[24]

Multivariate regression analysis in the present study identified hs-CRP and NT-proBNP as independent predictors of severe disease. These findings suggest that biomarker assessment could potentially serve as a useful adjunct for risk stratification and disease monitoring.

The overall findings of this study emphasize that pediatric RHD represents a dynamic inflammatory condition involving both valvular and myocardial pathology. Biomarkers such as hs-CRP and NT-proBNP may provide important prognostic information and facilitate early identification of patients at increased risk for progression.

Clinical Implications

hs-CRP and cardiac biomarkers may serve as simple, non-invasive adjunctive tools for early risk stratification, assessment of disease severity, monitoring progression, and identifying pediatric rheumatic heart disease patients at risk for myocardial dysfunction and adverse outcomes.

CONCLUSION:

The present study demonstrated significantly elevated levels of hs-CRP and cardiac biomarkers including Troponin-I, CK-MB, and NT-proBNP among pediatric patients with rheumatic heart disease compared with healthy controls. Increased biomarker levels showed significant association with disease severity, ventricular dysfunction, and echocardiographic abnormalities. Elevated hs-CRP supports the presence of persistent inflammatory activity, while increased cardiac biomarkers indicate ongoing myocardial stress and subclinical cardiac involvement. The progressive rise in biomarker concentrations with advancing disease severity suggests their potential role as adjunctive indicators for disease monitoring and prognostic assessment. Early identification of high-risk pediatric patients using these biomarkers may facilitate timely intervention and improved clinical outcomes.

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