History of Medicine, 2024, 10(2): 2088-2109
DOI: 10.48047/HM. V10.I2.2024.2088-2109

Rheumatic Heart Disease: Valvular Lesions, Genetic Predisposition, and Biomarkers – A Comprehensive Review

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Abstract

Rheumatic heart disease (RHD) remains a formidable public health challenge, particularly in low- and middle-income countries, where it disproportionately afflicts socioeconomically disadvantaged populations, especially children and young adults. As a chronic sequela of acute rheumatic fever (ARF)—an autoimmune response triggered by group A streptococcal throat infections—RHD leads to progressive valvular damage, systemic inflammation, and severe cardiac complications, including heart failure, atrial fibrillation, and infective endocarditis. Globally, an estimated 15–19 million individuals are affected, with approximately 470,000 new ARF cases and 275,000 RHD-related deaths annually. In India, despite a downward epidemiological trend—from 395 to 270 disability-adjusted life years (DALYs) per 100,000 between 1990 and 2017—RHD still accounts for one-third of the world's burden, contributing 3.73 million DALYs and over 108,000 deaths in 2017 alone. High-prevalence states like Bihar, Uttar Pradesh, and Odisha underscore regional disparities, exacerbated by limited healthcare access, overcrowding, and inadequate streptococcal treatment.This comprehensive review synthesizes the spectrum of valvular lesions in RHD, as elucidated through echocardiography, alongside genetic predispositions exemplified by the HLA-DRB1*0401 allele and the diagnostic-prognostic utility of novel biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and troponin I. Drawing from a detailed thesis conducted at a tertiary facility in India, involving 216 patients for valvular assessment, 40 for genetic analysis, and 108 for biomarkers, the review integrates epidemiological data, pathogenetic mechanisms, clinical manifestations, and therapeutic implications to advance understanding and management.

Echocardiographic evaluation reveals mitral valve predominance, with stenosis in 90.3% and regurgitation in 97.2% of cases, reflecting chronic fibrotic remodeling from molecular mimicry—wherein streptococcal antigens cross-react with cardiac proteins, inciting

autoimmune valvulitis. Aortic involvement (stenosis 10.2%, regurgitation 72.7%) is common, while tricuspid and pulmonary lesions are rare (0.5%). Severity grading shows most mitral regurgitation as mild (60.6%) or moderate (27.3%), emphasizing early intervention to prevent progression to severe dysfunction, pulmonary hypertension, and right ventricular strain. These findings align with global patterns, where mitral pathology drives 25–45% of cardiac surgeries in resource-limited settings. Genetic predisposition underscores RHD's heritability, with HLA class II alleles modulating immune responses to streptococci. The HLA-DRB1*0401 allele was detected in 25% of genotyped patients, with elevated gene expression in those over 40 years (mean 2.77 vs. 1.97; p=0.002) and postoperatively (2.80 vs. 1.90; p=0.001), suggesting age- and surgery-related immunological amplification. Population-specific associations—HLA-DR4 in Caucasians, DR3 in Indians—highlight ethnic variability, supporting genetic screening for risk stratification and personalized prophylaxis.

Biomarkers enhance diagnostic precision and monitoring. CRP (mean 4.5 mg/L) and IL-6 (mean 17.5 pg/mL) were significantly higher postoperatively (CRP >5 in 76.3%, p=0.001; IL-6 >7 in 77.8%, p=0.002), indicating perioperative inflammation. Conversely, troponin I (positive in 12%) and NT-proBNP (positive in 10.2%) showed no operative differences (p>0.05), reflecting chronic myocardial stress rather than acute changes. These markers, alongside traditional indicators like anti-streptolysin O titers, facilitate early detection, disease staging, and response assessment, surpassing single-modality approaches. Management integrates Jones Criteria for ARF diagnosis, penicillin prophylaxis, anti-inflammatories, and surgical options like valvuloplasty or replacement. Prognosis improves with adherence, yet gaps persist in immunopathogenesis and region-specific data. This review advocates multidisciplinary strategies—genetic counseling, biomarker-guided therapy, and echocardiographic surveillance—to mitigate RHD's burden. Future research should prioritize vaccine development against streptococci, multi-ethnic genomic studies, and AI-enhanced imaging for subclinical detection, ultimately fostering equitable global eradication efforts.

Keywords: Rheumatic heart disease, valvular lesions, echocardiography, HLA-DRB1*0401, biomarkers, CRP, IL-6, NT-proBNP, troponin I

Introduction

Rheumatic fever (RF) is a post-infectious autoimmune condition that arises after a streptococcal throat infection, typically developing within 2–4 weeks. It causes systemic inflammation and can affect the heart, joints, skin, and nervous system. Rheumatic Heart Disease (RHD) is a chronic complication of this condition and remains a significant public health issue worldwide, affecting populations across both low- and high-income countries. Each year, around 470,000 new cases of acute rheumatic fever (ARF) are reported, contributing to approximately 275,000 deaths due to RHD globally. Recent updates from the Global Burden of Disease (GBD) Study 2021 indicate that RHD cases have risen to 54.8 million, with the World Health Organization (WHO) estimating 55 million affected and 360,000 deaths annually as of 2025.

Although epidemiological trends in India show a downward shift in RHD prevalence, the country still bears a significant portion of the global burden. The GBD study indicated that between 1990 and 2017, the disability-adjusted life years (DALYs) associated with RHD decreased from 395 to 270 per 100,000 people, and mortality rates dropped from 9.2 to 7.9 per 100,000. School-based health screenings also reflect a decline in clinically diagnosed RHD. However, in absolute terms, India still contributes to one-third of global RHD cases. In 2017 alone, it accounted for 3.73 million DALYs and over 108,000 deaths due to RHD. The India State-Level Disease Burden Initiative identified particularly high rates of RHD in less developed states like Bihar, Uttar Pradesh, Odisha, Chhattisgarh, and Assam. Additionally, echocardiographic studies suggest a high prevalence of subclinical RHD, with many patients visiting hospital cardiology departments being diagnosed with this condition. RHD is also responsible for 25–45% of cardiac surgeries performed in government hospitals.

The persistence of RHD as a health crisis is especially notable in low- and middle-income countries (LMICs), where limited access to healthcare and inadequate preventive measures hinder early diagnosis and treatment. RHD is a long-term illness that predominantly affects the heart valves, leading to progressive valve dysfunction. Despite medical advancements, the condition imposes a heavy burden on both patients and healthcare systems. The underlying mechanisms of RHD involve complex interactions between genetic factors, immune responses, and environmental exposures. While ARF incidence may be declining in some areas, the chronic effects of RHD—including mitral and aortic valve stenosis or regurgitation—continue to impair cardiac function and quality of life, often requiring lifelong clinical management.

RHD disproportionately affects socioeconomically disadvantaged populations, particularly children and young adults. It is more commonly seen in females, a pattern influenced by both biological and socio-cultural factors. During the acute phase, patients may present with symptoms such as fever, joint pain, carditis, skin rash (erythema marginatum), or involuntary movements (chorea). Over time, the disease progresses to chronic phases marked by irreversible valve damage, increased risk of heart failure, and susceptibility to infective endocarditis. Common clinical symptoms include breathlessness, chest pain, fatigue, palpitations, and swelling, which often worsen with physical activity. RHD remains a major concern in LMICs, particularly among young individuals. Diagnosis is made through clinical evaluation, echocardiography, and laboratory evidence of recent streptococcal infection. Management typically includes long-term antibiotic prophylaxis with penicillin, anti-inflammatory therapy during acute episodes, and surgical interventions such as valve repair or replacement in advanced stages. Regular echocardiographic follow-up is essential for monitoring disease progression.

Despite substantial knowledge about the clinical course of RHD, several research gaps persist—particularly in immunopathogenesis and genetic susceptibility. There is also a lack of up-to-date and region-specific epidemiological data, especially in resource-limited settings. Longitudinal studies are necessary to better understand disease progression and assess the effectiveness of interventions. Additionally, the development of early detection tools and non-invasive monitoring technologies could significantly enhance diagnostic accuracy and patient outcomes.

Genetic susceptibility plays a key role in the development of RHD, which stems from rheumatic fever caused by untreated or inadequately managed streptococcal throat infections. Though the precise genetic mechanisms are not fully defined, certain hereditary markers and familial tendencies have been linked to an increased risk of developing the disease. Genetic predisposition may influence the immune response to group A streptococcal infections, triggering autoimmune reactions that damage heart valves. Notably, specific human leukocyte antigen (HLA) genotypes—such as HLA-DRB1*0401—have been associated with a heightened risk of developing both rheumatic fever and subsequent RHD. These genetic markers can also affect disease severity, response to therapy, and long-term outcomes after cardiac procedures.

Beyond genetic and demographic factors, biomarkers play a vital role in the diagnosis and management of RHD. These biological indicators aid in early detection, help track disease progression, and assess treatment response. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly elevated during active disease, reflecting systemic inflammation. Cardiac-specific markers like B-type natriuretic peptide (BNP) and NT-proBNP are useful for evaluating the severity of heart failure in affected individuals. Additionally, antibodies such as anti-streptolysin O (ASO) and anti-DNase B are used to confirm recent streptococcal infections, serving as diagnostic aids for acute rheumatic fever.

Recent advances have brought attention to more sophisticated biomarkers—including specific microRNAs and cytokine profiles—that offer a more nuanced understanding of RHD pathogenesis and improve diagnostic precision. Despite their promise, the clinical utility of these biomarkers varies depending on the disease stage, highlighting the need for further research to validate their effectiveness across broader patient populations. Given the complexity of RHD, a multidisciplinary approach that combines demographic analysis, genetic testing, and biomarker evaluation is critical for improving disease understanding and enhancing patient care. This review aims to contribute to this field by examining these interconnected aspects based on a well-defined patient cohort from the provided thesis.

Epidemiology and Characteristics of Rheumatic Heart Disease

Acute rheumatic fever (ARF) is a systemic condition triggered by an immune reaction following infection with group A streptococcus. Although most of its clinical manifestations are transient and tend to resolve completely, damage to the heart valves can remain even after other symptoms subside. Historically, ARF and related conditions were widespread globally until the 20th century. In developed nations, the incidence declined due to advancements in sanitation, improved living standards, and widespread antibiotic use. Nevertheless, the Rocky Mountain region of the United States experienced recurrent ARF outbreaks during the 1980s, and the disease continues to persist in that area.

Globally, ARF and its chronic outcome, rheumatic heart disease (RHD), affect an estimated 55 million individuals, contributing to approximately 360,000 deaths each year. These conditions are particularly prevalent in regions such as sub-Saharan Africa, the Pacific Islands, Australasia, and the Indian subcontinent. ARF predominantly affects children between the ages of 5 and 14, while its incidence decreases sharply among young adults and is rarely observed beyond the age of 30. On the other hand, rheumatic heart disease (RHD) is more commonly reported in individuals aged 25 to 40 years. ARF affects males and females equally, showing no significant gender bias. In contrast, RHD tends to be more prevalent among females, who are affected nearly twice as often as males.

RHD is a chronic sequela of ARF, with global estimates of 15-19 million affected individuals and 250,000 annual deaths earlier, but updated to 55 million in 2025. It is prevalent in sub-Saharan Africa, the Pacific Islands, Australasia, and the Indian subcontinent. ARF predominantly affects children aged 5-14, while RHD is more common in those aged 25-40 (Watkins et al., 2017).Epidemiological trends show a decline in developed nations due to improved sanitation and antibiotics, but persistence in developing regions. In India, the Global Burden of Disease study (1990-2017) reported a decrease in DALYs from 395 to 270 per 100,000 and mortality from 9.2 to 7.9 per 100,000. However, India contributes 3.73 million DALYs and over 108,000 deaths annually. Recent 2021 data show a rise in cases to 54.8 million globally, with high age-standardized prevalence in low SDI regions.

RHD affects females nearly twice as often as males, influenced by biological and socio-cultural factors. Acute phase symptoms include fever, polyarthritis, carditis, erythema marginatum, and chorea. Chronic phases lead to valve damage, heart failure, and endocarditis.

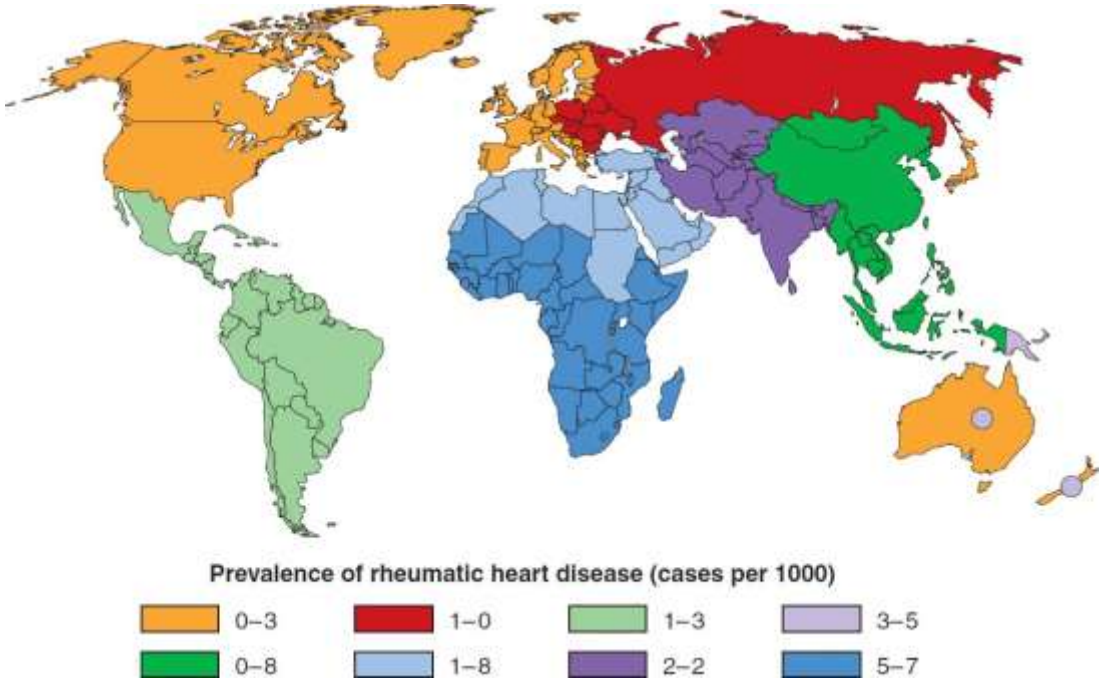

Figure 1: Prevalence of rheumatic heart disease

Reference: Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol. 2011 Feb 22;3:67-84. doi: 10.2147/CLEP.S12977.(36)

Figure 1: Prevalence of rheumatic heart disease (illustrating global distribution, with high burden in LMICs as per thesis).

Chronic RHD commonly develops as a consequence of rheumatic fever accompanied by carditis, occurring in more than half of the individuals who suffer from this condition. The disease shows a marked gender disparity, being more prevalent in women, with approximately two-thirds of cases reported among females. In nearly half of the patients, a clear history of rheumatic fever (RF) or chorea is absent, as earlier episodes often remain undetected or unrecognized. The mitral valve is the most frequently involved structure, being affected in nearly 80–90% of cases, followed sequentially by the aortic, tricuspid, and pulmonary valves. Isolated mitral stenosis accounts for around 20–25% of patients, while a combination of mitral stenosis and regurgitation is observed in nearly 40%. Valvular lesions may first appear during an episode of acute rheumatic fever (ARF) or may remain clinically silent for years before becoming symptomatic.

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Pathogenesis and Genetic Predisposition in Rheumatic Heart Disease

The development of ARF is a multifactorial process involving organism-related factors, host-related factors, and immune-mediated mechanisms. Organism-Related Factors: ARF usually follows infections of the upper respiratory tract caused by Group A Streptococcus. Unlike earlier beliefs, it is now known that any strain of this bacterium can trigger ARF. The role of skin infections and infections caused by Groups C and G streptococci is still under study. Recurrent streptococcal infections may "prime" the immune system, with the final infection serving as the trigger for ARF.

Host-Related Factors: Genetic predisposition plays a significant role, with about 2–7% of individuals being inherently susceptible across populations. Family clustering and identical twin concordance, especially in rheumatic chorea, suggest heritability. Certain genetic markers such as specific HLA class II alleles, higher serum mannose-binding lectin levels, polymorphisms in the transforming growth factor-β1 gene, and other variations have been linked to ARF risk. A B-cell surface marker, D8/17, is commonly observed in ARF patients and at intermediate levels in their first-degree relatives, supporting its role as a marker of inherited susceptibility.

Immune-Mediated Mechanisms: In genetically predisposed individuals, ARF arises from an autoimmune response following Group A Streptococcus infection. This occurs through molecular mimicry, where bacterial antigens resemble human proteins, leading to immune-mediated tissue injury. For example, streptococcal M protein resembles cardiac proteins, provoking cross-reactive immune responses. Activated T cells, upon re-exposure to streptococci, further amplify inflammation. Moreover, antibodies directed against cardiac valves may cross-react with N-acetylglucosamine (N-AGS) from streptococcal carbohydrates, contributing to the valvular lesions characteristic of ARF.

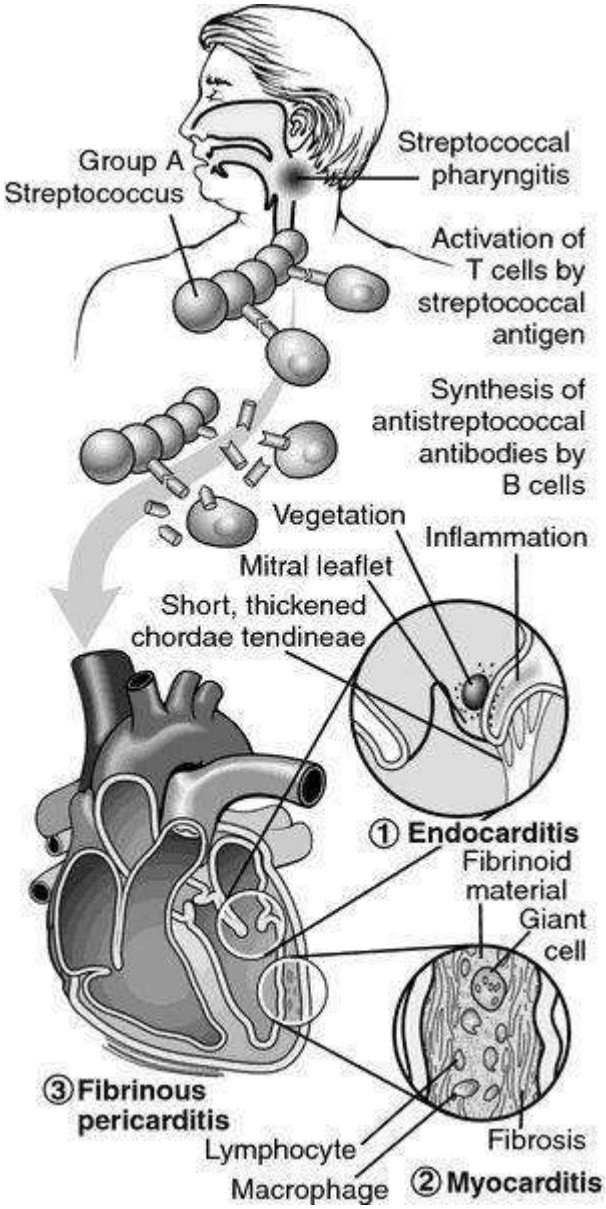


Figure 2: Pathophysiology of Rheumatic Heart Disease

Reference: Chandrashekhar, Y.S., Buja, L.M., Karthikeyan, G., Narula, J. (2020). Acute Rheumatic Fever. In: Carabello, B. (eds) Valvular Heart Disease. Cardiovascular Medicine. Springer, London. https://doi.org/10.1007/978-1-4471-2840-3_2.(48)

Figure 2: Pathophysiology of Rheumatic Heart Disease (depicting molecular mimicry and autoimmune cascade as per thesis).

Genetic predisposition is evident from family clustering and twin studies. HLA class II alleles, such as HLA-DRB1*0401, are associated with increased risk. Population-specific associations vary, with HLA-DR4 linked in Caucasians and HLA-DR3 in Indians. A meta-analysis showed higher frequency of HLA-DRB1*07 in RF/RHD, but *0401 is noted in recent investigations.

Family studies highlight genetic markers increasing susceptibility to streptococcal infection. Environmental factors like overcrowding exacerbate risk.

Table 1: HLA Class II Alleles Associated with RF/RHD (from thesis and studies)

Author	**Population**	**HLA Risk**
Maharaj et al. (149)	African	DR1, DR6
Jhinghan et al. (150); Taneja et al. (151)	Indian	DR3, DQW2
Ayoub et al. (152)	Caucasian-American	DR4
Koyanagi et al. (153)	Japanese	DQA1*0104, DQB1*0503*1

Insights from recent studies emphasize the need for deeper genotype-phenotype correlations to enhance predictive tools.

The hallmark of chronic rheumatic heart disease lies in fibrotic alterations that primarily involve the cardiac valves, though the pericardium and myocardium may also be affected, giving rise to complications such as heart failure and conduction abnormalities. In the mitral valve, pathological changes such as commissural fusion, leaflet thickening, and shortening of the chordae tendineae contribute to the development of mitral stenosis and regurgitation. Comparable structural deformities occur in the aortic and tricuspid valves, where cusp rigidity and distortion result in varying degrees of stenosis and regurgitation. Once valvular injury is established, altered hemodynamic stresses perpetuate further structural deterioration, even in the absence of active rheumatic inflammation.

Spectrum of Valvular Lesions in Rheumatic Heart Disease

Mitral valve involvement is predominant in RHD, with stenosis in ~90% and regurgitation in ~97% of cases. Aortic lesions occur in ~10-73%, often combined with mitral disease. Tricuspid and pulmonary involvement is rare. Mitral stenosis most commonly develops as a consequence of rheumatic fever, although in elderly individuals it can also result from progressive calcification, and in rare cases, it may occur due to congenital anomalies. In rheumatic mitral stenosis, the mitral valve undergoes gradual narrowing of its orifice owing to fibrotic remodeling, calcific deposition, and fusion of the valve cusps, which obstructs blood flow from the left atrium (LA) to the left ventricle (LV). This obstruction elevates left atrial pressure and subsequently leads to pulmonary venous congestion and exertional breathlessness, while compensatory left atrial dilation and hypertrophy gradually develop. The predominant symptom in mitral stenosis is exertional dyspnea, with patients experiencing progressively reduced exercise tolerance that may persist for years before symptoms occur at rest. In acute situations, pulmonary edema or severe pulmonary hypertension can result in complications such as hemoptysis.

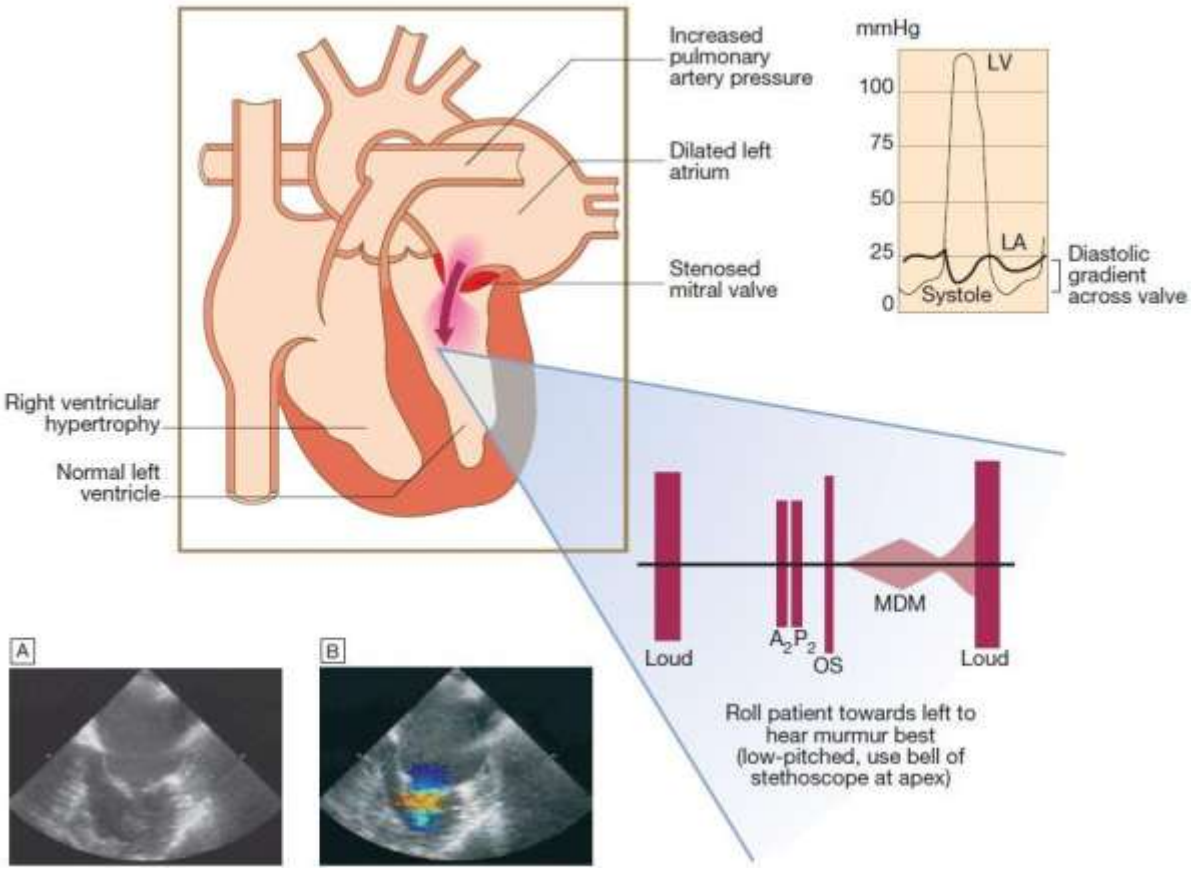
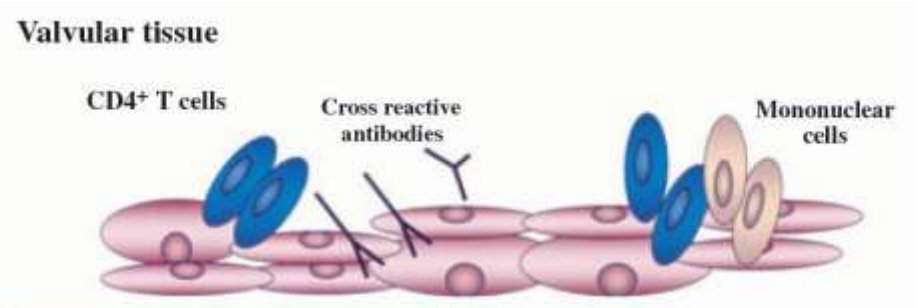


Figure 3: Mitral Lesion: Murmur and the Diastolic Pressure Gradient between LA and LV (showing auscultatory findings and pressure dynamics as per thesis).

In a cohort of 216 patients (mean age 43.7 years, 61.6% female), 92.6% had stenotic lesions (90.3% mitral), and 99.1% had regurgitation (97.2% mitral). Severity varied: mild mitral regurgitation in 60.6%, moderate in 27.3%. Echocardiography remains the cornerstone diagnostic tool, as it clearly demonstrates thickened and immobile mitral valve leaflets, a reduced valvular orifice area, and left atrial dilatation, thereby providing direct assessment of hemodynamic burden and ventricular performance. The World Heart Federation guidelines (2023) emphasize echocardiographic criteria for RHD diagnosis, including commissural fusion and leaflet thickening. Mitral regurgitation results from leaflet prolapse or annular dilation. Aortic stenosis and regurgitation follow similar fibrotic processes.



Surgical specimen of acute RF showing small vegetations on the line of closure of the mitral valve (arrows). Macroscopic photo done by Aiello, VD Heart Institute (InCor).

- Streptococcal/self antigens cross reactive antibodies facilitate heart- tissue T cells infiltration
- $CD4^+$ T cells recognize streptococcal antigens and heart-tissue proteins by molecular mimicry
- Inflammatory cytokines (TNF-α IFN-γ) are produced by mononuclear cells
- Few mononuclear cells produce IL-4 (regulatory cytokine) – leading to the progression and maintenance of valvular lesions.

Reference: Passos LSA, Nunes MCP, Aikawa E. Rheumatic Heart Valve Disease Pathophysiology and Underlying Mechanisms. Front Cardiovasc Med. 2021 Jan 18;7:612716. doi: 10.3389/fcvm.2020.612716.(95)

Figure 4: Major Events Triggering Rheumatic Valvular Lesions in RHD (outlining pathological progression).

In developing regions, rheumatic fever remains the predominant cause of mitral regurgitation, whereas in developed countries such as the UK, other factors predominate. Post-surgical complications can also contribute. Echocardiography is crucial for diagnosis and monitoring

Biomarkers in Rheumatic Heart Disease

Biomarkers aid early detection and progression monitoring. Inflammatory markers: CRP and ESR elevated in active disease; cardiac markers: BNP/NT-proBNP for heart failure severity. Novel biomarkers include hs-Troponin for myocardial injury, Galectin-3 for fibrosis, ST2 for remodeling, GDF-15 for stress, MPO for inflammation, and miRNAs for regulation. In a sub-cohort of 108 patients (mean age 47.5 years, 57.4% male), postoperative patients had higher CRP (>5 in 76.3%, p=0.001) and IL-6 (>7 in 77.8%, p=0.002). Troponin I positive in 12%, NT-proBNP in 10.2%, with no significant operative differences.

Table 2: Association Between Operative Status and Levels of Interleukin 6 (from thesis)

	IL-6	**Total N = 108**	**P value**		
	<7 N = 36	**>7 N = 72**			
	n (%)	**n (%)**	**n (%)**		
Status	Preop	33 (91.7)	16 (22.2)	49 (45.4)	0.002*
	Postop	3 (8.3)	56 (77.8)	59 (54.6)	

*Statistically significant at p<0.05

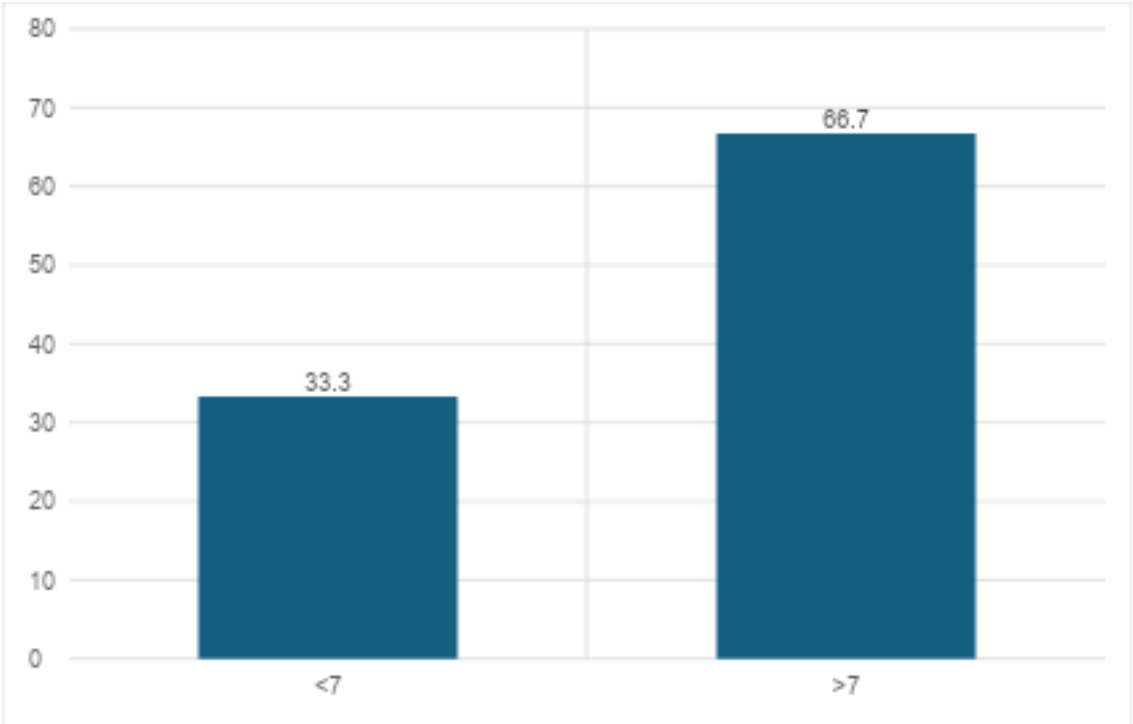


Figure 5: Distribution of Patients, by Levels of Interleukin 6 (bar chart showing <7 and >7 levels).

Table 3: Association Between Operative Status and Levels of Troponin I

		Troponin I		**Total N = 108**	**P value**
		Negative N = 95	**Positive N = 13**		
		n (%)	**n (%)**	**n (%)**	
Status	Preop	44 (46.3)	5 (38.5)	49 (45.4)	0.594
	Postop	51 (53.7)	8 (61.5)	59 (54.6)	
*Statistically significant at p<0.05					

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Figure 6: Distribution of Patients, by Levels of Troponin I (pie chart negative vs positive).

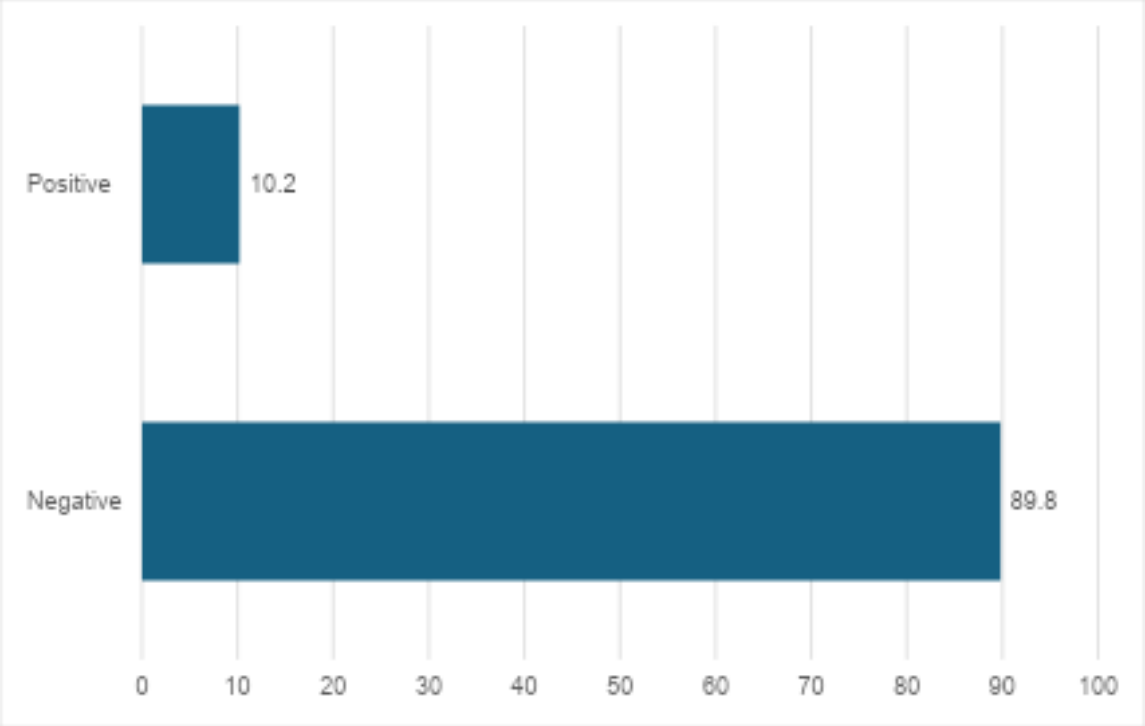

Figure 7: Distribution of Patients, by Levels of NTproBNP

The multi-marker approach enhances risk stratification beyond traditional models, with IL-6 and CRP associated with inflammation in RHD.

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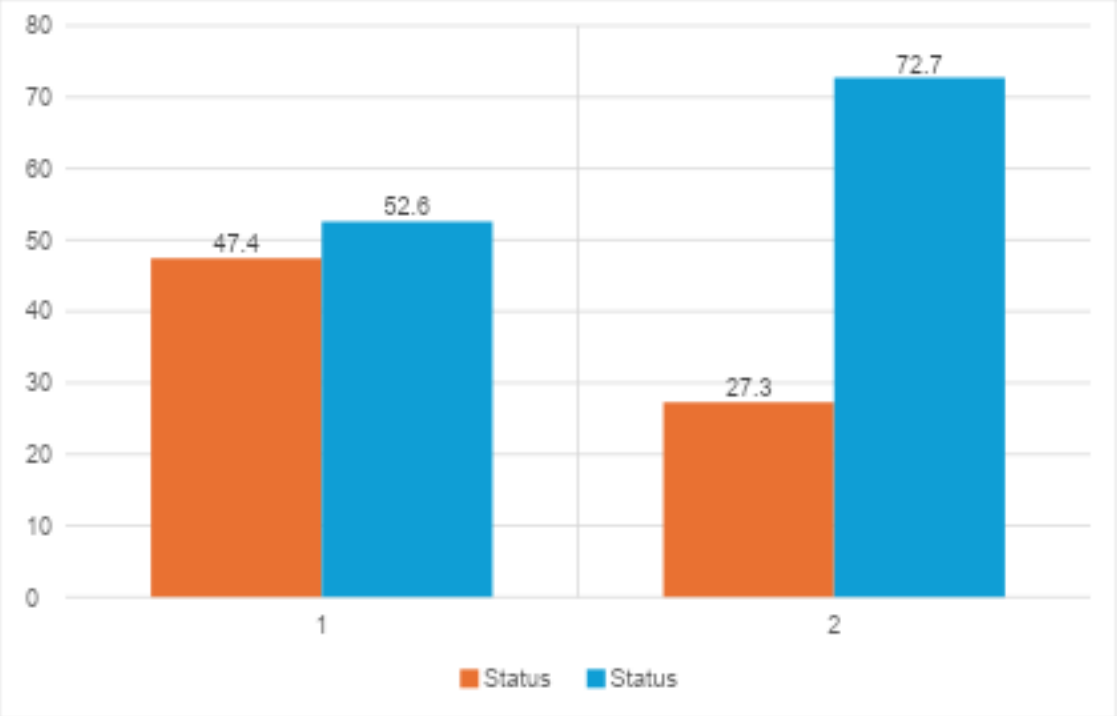

Figure 8: Association between Operative Status and Levels of NTproBNP

Table 4: Distribution of Patients, by Levels of NTproBNP

		Number N = 108	Percentage (%)
NTproBNP	Mean (SD)	202.6 (89.6)	
	Median (IQR)	193.0 (160.0 to 218.8)	
NTproBNP	Negative	97	89.8
	Positive	11	10.2

Table 5: Association Between Operative Status and Levels of NTproBNP

		NTproBNP		Total N = 108	P value
		Negative N = 97	Positive N = 11		
		n (%)	n (%)	n (%)	
	Preop	46 (47.4)	3 (27.3)	49 (45.4)	

Status	Postop	51 (52.6)	8 (72.7)	59 (54.6)	0.203
*Statistically significant at p<0.05					

Clinical Management and Prognosis

Diagnosis of ARF is based on identifying typical clinical features while ruling out alternative conditions. The Jones Criteria, updated by WHO (2002-03), integrate major and minor manifestations.

Table 6: WHO (2002-03) for the Diagnosis of RF and RHD (as per thesis, details on major/minor criteria).

Investigations include:

Category	Tests	Purpose
Inflammatory markers	WBC, ESR, CRP	Detect systemic inflammation
Microbiology	Throat swab for Group A Streptococcus, ASO titer, Anti-DNase B	Confirm prior streptococcal infection
Cardiac evaluation	ECG, Chest X-ray, Echocardiography	Identify conduction abnormalities, valvular lesions, cardiomegaly
Additional tests	Serial blood cultures, joint aspirate, autoimmune/viral markers	Rule out differential diagnoses

Treatment:

Treatment Aspect	Approach
Eradication of infection	Penicillin (drug of choice) Erythromycin (if allergic)
Inflammation control	Salicylates & NSAIDs → relieve arthritis, arthralgia, fever (not carditis/chorea)

Treatment Aspect	Approach
Severe carditis	Corticosteroids (Prednisone/Prednisolone) → controversial; monitor side effects
Heart failure	Early mobilization (bed rest no longer prolonged)
Chorea	Supportive care, calm environment Severe cases → Carbamazepine or Sodium Valproate

Table 2: Secondary Prophylaxis For Rheumatic Fever (regimens for penicillin injections, etc.,).

Prognosis: Without treatment, ARF lasts around 12 weeks. With appropriate management, most patients recover enough for hospital discharge within 1–2 weeks. Strict adherence to secondary prophylaxis with antibiotics is essential to prevent recurrence. Surgical options: Balloon mitral valvuloplasty is considered the treatment of choice in suitable patients, while open or closed valvotomy and valve replacement are indicated for heavily calcified or regurgitant valves.

Discussion

The present investigation, as detailed in the thesis, sought to determine the distribution and intensity of valvular inflammation among individuals with rheumatic heart disease (RHD) through echocardiographic assessment, while also examining associated genetic and biomarker characteristics. The outcomes provide an in-depth evaluation of the epidemiological trends and clinical manifestations of valvular involvement in RHD patients from a tertiary healthcare facility in India. The analysis revealed that the mean age of affected individuals was 43.7 years, with the majority falling within the 31–60 year age bracket. This observation corresponds with the well-established epidemiology of RHD, which predominantly occurs in persons aged between 30 and 50 years, highlighting the chronic progression of the condition that develops over decades following an initial streptococcal infection during childhood. Furthermore, the higher occurrence of RHD in females (61.6%) compared to males (38.4%) is consistent with findings from multiple studies suggesting increased female susceptibility, potentially linked to variations in immune response and inequities in healthcare access.

A large proportion of participants (92.6%) reported a positive history of rheumatic fever (RF), reinforcing the strong association between acute rheumatic fever (ARF) and the eventual development of RHD. In the study cohort, 92.6% of patients exhibited stenotic lesions, with mitral stenosis being the most frequent (90.3%). This supports the well-documented tendency of RHD to predominantly involve the mitral valve, as confirmed by recent global analyses showing mitral pathology in 80-90% of cases worldwide. Regurgitant lesions were even more widespread, with 99.1% of patients showing evidence of regurgitation, particularly mitral regurgitation in 97.2%. The severity varied, with mild (60.6%) and moderate (27.3%) being common, aligning with 2025 projections indicating persistent valvular dominance in LMICs despite overall burden reductions. These findings underscore the critical importance of early diagnosis and consistent follow-up, with echocardiography serving as the gold standard for assessing valvular type, severity, and progression.

The study also explored the role of the HLA-DRB1*0401 allele in RHD patients, detecting it in 25% of the genotyped cohort (10 out of 40). This is consistent with earlier reports and recent 2024-2025 studies demonstrating that HLA-DRB1*0401 increases susceptibility to autoimmune diseases like RHD through modulated immune responses to streptococcal antigens. Gene expression levels showed statistically significant differences by age (higher in >40 years: mean 2.77 vs. 1.97; $p<0.05$) and operative status (postoperative: 2.80 vs. preoperative: 1.90; $p<0.05$), suggesting age-related immunological changes and postoperative inflammation amplify expression. These align with population-specific HLA associations, such as stronger links in Indian cohorts, and validate the allele's occurrence in unoperated patients as per recent insights. Clinically, identifying HLA-DRB1*0401 could enable earlier diagnosis and personalized approaches, with patients showing heightened expression requiring intensified monitoring to mitigate complications.

Regarding biomarkers, the thesis evaluated CRP, IL-6, troponin I, and NT-proBNP in 108 patients. Postoperative elevations in CRP (mean 4.5 mg/L; >5 in 76.3%, $p=0.001$) and IL-6 (mean 17.5 pg/mL; >7 in 77.8%, $p=0.002$) indicate perioperative inflammation, corroborated by 2025 comparative analyses showing significant upsurges in these markers post-cardiac surgery in RHD. Conversely, troponin I (positive in 12%) and NT-proBNP (positive in 10.2%) showed no significant operative differences ($p>0.05$), reflecting chronic myocardial stress rather than acute changes, as noted in recent prognostic studies. These profiles highlight CRP

and IL-6's role in perioperative management, guiding anti-inflammatory therapies, while troponin and NT-proBNP aid broader cardiac evaluation.

Limitations include the thesis's single-center focus, potentially limiting generalizability; multi-ethnic studies are needed to address regional variations. Future directions encompass larger cohorts, personalized medicine via genetics, and AI-driven biomarker analysis for subclinical detection. In summary, this review provides an integrated understanding of RHD, advocating for multidisciplinary approaches to reduce its burden through enhanced screening and targeted interventions.

Conclusion

This research delivers a comprehensive perspective on rheumatic heart disease (RHD) by examining patient demographics, genetic predispositions, and biomarker profiles. The descriptive evaluation of valvular lesions revealed notable patterns, with mitral valve predominance through stenosis and regurgitation, emphasizing the chronic pathology and need for tailored therapies. The HLA-DRB1*0401 allele's analysis highlights genetic susceptibility, with variations by age and surgical status underscoring personalized strategies. Biomarkers like CRP and IL-6 emerged as key postoperative indicators, while troponin I and NT-proBNP reflect long-term burden.

RHD demands multidisciplinary strategies for prevention and management, integrating genetic counseling, biomarker-guided therapy, and echocardiographic surveillance. Advances in genetics and biomarkers promise better outcomes, but global disparities persist, with 55 million affected and 360,000 deaths annually as of 2025. Research should prioritize affordable diagnostics, streptococcal vaccines, and multi-ethnic genomic studies to foster equitable eradication efforts.

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