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Spectrum of Valvular Lesions in Rheumatic Heart Disease by Echocardiography with Genetic Interpretation

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Abstract
Rheumatic Heart Disease (RHD) remains a significant public health concern globally, particularly in low- and middle-income countries, contributing to substantial morbidity and mortality. This hospital-based cross-sectional study, conducted at a tertiary healthcare facility in India, aimed to investigate the distribution of valvular lesions in RHD patients, evaluate the role of the HLA-DRB1*0401 allele, and assess novel biomarkers (C-reactive protein, IL-6, NT-proBNP, and troponin I). Among 216 patients, mitral stenosis and regurgitation were predominant (90.3% and 97.2%, respectively), with a higher prevalence in females (61.6%) and middle-aged individuals (31–60 years). The HLA-DRB10401 allele was detected in 25% of a subgroup of 40 patients, showing elevated gene expression in postoperative and older patients. Postoperative patients exhibited significantly higher CRP and IL-6 levels, indicating persistent inflammation, while troponin I and NT-proBNP did not vary by operative status. These findings underscore the need for early genetic screening and biomarker monitoring to improve RHD management. The study highlights RHD's multifactorial nature, advocating multidisciplinary approaches to reduce its burden.

Keywords:- Rheumatic Heart Disease, Valvular Lesions, HLA-DRB1*0401, Biomarkers, Echocardiography, Mitral Stenosis, Genetic Susceptibility, Postoperative Inflammation

Introduction

Overview of Rheumatic Fever and Rheumatic Heart Disease

Rheumatic Fever (RF) is an autoimmune inflammatory condition triggered by an immune response to group A streptococcal (GAS) pharyngitis, typically manifesting 2–4 weeks post-infection. It affects multiple organ systems, including the heart, joints, skin, and central nervous system, leading to complications such as Rheumatic Heart Disease (RHD), a chronic condition characterized by progressive valvular damage. RHD remains a significant global health challenge, particularly in low- and middle-income countries (LMICs), where access to healthcare and preventive measures is limited (Watkins et al., 2018). Globally, RF contributes to approximately 470,000 new cases annually, resulting in 275,000 RHD-related deaths (Watkins et al., 2018). In India, RHD accounts for one-third of the global burden, with 3.73 million disability-adjusted life years (DALYs) and over 108,000 deaths in 2017 (India State-Level Disease Burden Initiative, 2017). Despite a decline in RHD prevalence, as evidenced by a reduction in DALYs from 395 to 270 per 100,000 and mortality from 9.2 to 7.9 per 100,000 between 1990 and 2017 (GBD Study, 2018), India continues to face a high burden, particularly in less-developed states like Bihar, Uttar Pradesh, Odisha, Chhattisgarh, and Assam. Echocardiographic screening reveals a significant subclinical prevalence, suggesting underdiagnosis in clinical settings (Marijon et al., 2012).

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Epidemiological Trends and Regional Disparities

The decline in RHD prevalence in India reflects improvements in healthcare access, antibiotic use, and living conditions, yet the disease persists in socioeconomically disadvantaged regions. School-based screenings indicate a reduction in clinically diagnosed cases, but echocardiographic studies highlight a high prevalence of subclinical RHD, particularly in resource-limited settings (Kumar & Tandon, 2013). RHD contributes to 25–45% of cardiac surgeries in government hospitals, underscoring its impact on healthcare systems (Marijon et al., 2012). The persistence of RHD in states like Bihar and Uttar Pradesh is linked to poverty, overcrowding, and inadequate treatment of streptococcal infections, which exacerbate the risk of RF progressing to RHD (India State-Level Disease Burden Initiative, 2017).

Clinical Characteristics and Vulnerable Populations

RHD disproportionately affects children, young adults, and socioeconomically disadvantaged populations, with a notable female predominance (61.6% in the study cohort) attributed to biological and socio-cultural factors (Guilherme & Kalil, 2010). Hormonal influences, such as estrogen's role in modulating immune responses, may increase female susceptibility to autoimmune conditions like RHD (Parnaby & Carapetis, 2010). Socio-cultural barriers, including delayed healthcare access and prioritization of male health in some communities, further exacerbate the risk for women (Negi et al., 2020). Clinical symptoms of RHD include exertional dyspnea, chest pain, fatigue, palpitations, and edema, often progressing to heart failure if untreated. The mitral valve is most commonly affected (90.3% stenosis, 97.2% regurgitation), followed by the aortic valve (10.2% stenosis, 72.7% regurgitation), due to its anatomical susceptibility to autoimmune damage via molecular mimicry (Carapetis, 2007). Diagnosis relies on echocardiography, which detects valvular lesions, and laboratory tests confirming prior streptococcal infection (e.g., ASO, anti-DNase B titers) (Reményi et al., 2012).

Genetic Predisposition

Genetic factors play a critical role in RHD susceptibility. The HLA class II alleles, particularly HLA-DRB1*0401, are associated with increased risk due to molecular mimicry, where streptococcal antigens resemble cardiac proteins, triggering autoimmune responses (Guilherme & Kalil, 2010). In the study, 25% of a subgroup of 40 patients tested positive for HLA-DRB1*0401, with higher gene expression in postoperative patients ($p=0.001$) and those over 40 years ($p=0.002$) (Stanevicha et al., 2003). This suggests that genetic screening could identify at-risk individuals for early intervention, potentially improving outcomes through personalized medicine (Abdallah et al., 2021).

Role of Biomarkers

Biomarkers are essential for diagnosing and monitoring RHD. Inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6) were significantly elevated in postoperative patients ($p<0.05$), reflecting surgical inflammation (Pepys & Hirschfield, 2003; Mihara et al., 2012). Cardiac-specific markers, NT-proBNP and troponin I, showed no significant difference by operative status ($p>0.05$), indicating their utility in assessing chronic cardiac stress rather than acute surgical changes (Januzzi et al., 2006; Keller et al., 2009). Emerging biomarkers, such as microRNAs and galectin-3, hold promise for enhancing diagnostic precision but require further validation (Tijsen et al., 2010; de Boer et al., 2011).

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Management and Challenges

RHD management includes antibiotic prophylaxis (penicillin), anti-inflammatory therapy, and surgical interventions like valve repair or replacement. Echocardiography is crucial for monitoring disease progression (Reményi et al., 2012). Challenges include limited healthcare access in LMICs, high costs of diagnostics and surgery, and the need for region-specific epidemiological data. Multidisciplinary approaches integrating genetic screening, biomarker monitoring, and affordable diagnostics are essential to reduce the RHD burden (Carapetis et al., 2016).

Materials and Methods

Study Design

This hospital-based analytical study adopted a cross-sectional design.

Study Settings

The research was conducted at a tertiary healthcare facility in India.

Study Participants

The study population consisted of all patients presenting to the facility.

Inclusion Criteria

- Confirmed chronic RHD diagnosis via echocardiography-based screening.
- Patients in preoperative or postoperative stages.

Exclusion Criteria

- Congenital valvular abnormalities.

Sample Size

The sample size was calculated using the formula for estimating a proportion with specified absolute precision: (n = \frac{Z^2 \cdot p \cdot (1-p)}{L^2}), where (Z = 1.96) (95% confidence level), (p = 0.5) (maximum variability), and (L = 0.07) (precision). The calculated sample size was 196, rounded up to 216 to account for a 10% dropout rate.

Data Collection

- Demographic data: Age, gender, history of rheumatic fever.
- Echocardiography: Valvular involvement (stenosis/regurgitation), severity.
- Genetic Testing: Genomic DNA extracted from blood; HLA-DRB1 genotyping via PCR-SSO or allele-specific PCR (Olerup et al., 1992; Sallakci et al., 2005). HLA-DRB1*0401 detected using SSP with primers (Erlich et al., 1991; Hasegawa et al., 1985).
- Biomarker Estimation:
  - IL-6: ELISA on frozen serum.
  - CRP: Latex-enhanced nephelometry (Pepys & Hirschfield, 2003).
  - NT-proBNP: ECL-based RIA (Januzzi et al., 2006).
  - Troponin I: High-sensitivity CLIA on Cobas Integra (Thygesen et al., 2018).

Statistical Analysis

Data were entered into Excel and analyzed using SPSS version 23. Categorical data: frequencies/percentages; continuous data: mean ± SD or median (IQR). Comparisons: Chi-square/Fisher's exact for categorical, t-test for continuous variables. $P < 0.05$ considered significant.

Results

1.0 Descriptive Analysis of Valvular Lesions

The mean age was 43.7 ± 15.1 years (median: 43, IQR: 32.8–55.0, range: 10–83). Age distribution: 20.8% ≤30 years, 64.4% 31–60 years, 14.8% >60 years (Table 1, Figure 1). Females

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comprised 61.6%, males 38.4% (Table 2, Figure 2). All participants were from the study facility. 92.6% had a positive RF history **(Table 3, Figure 3).** Stenosis affected 92.6% (mitral: 90.3%, aortic: 10.2%, tricuspid: 0.5%; Table 4, Figure 4). Regurgitation affected 99.1% (mitral: 97.2%, aortic: 72.7%, tricuspid: 0.5%; Table 5, Figure 5). Mitral regurgitation severity: trivial 4.2%, mild 60.6%, moderate 27.3%, severe 5.1%, absent 2.8% (Table 6, Figure 6). Aortic regurgitation: trivial 30.6%, mild 42.1%, absent 27.3% (Table 7, Figure 7).

Table 1: Distribution of Patients, by Age (in years)

		Number N = 216	**Percentage (%)**
Age (n years)	Mean (SD)	43.7 (15.1)	
	Median (IQR)	43 (32.8 to 55.0)	
Age (in years)	≤30	45	20.8
	31 to 60	139	64.4
	More than 60	32	14.8
SD, Standard deviation; IQR, Interquartile range			

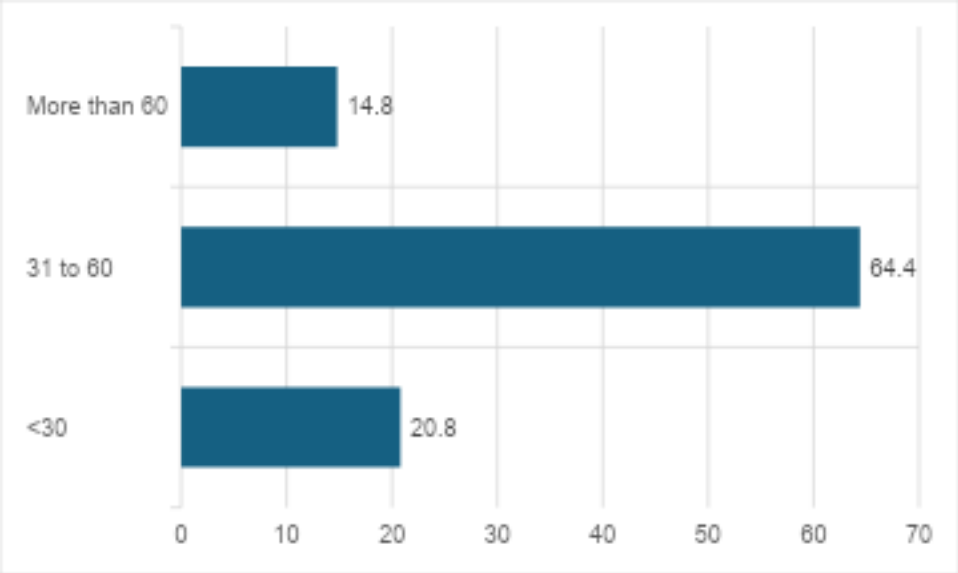

Figure 1: Distribution of Patients, by Age (in years)

Table 2: Distribution of Patients, by Gender

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		Number N = 216	Percentage (%)
Gender	Female	133	61.6
	Male	83	38.4

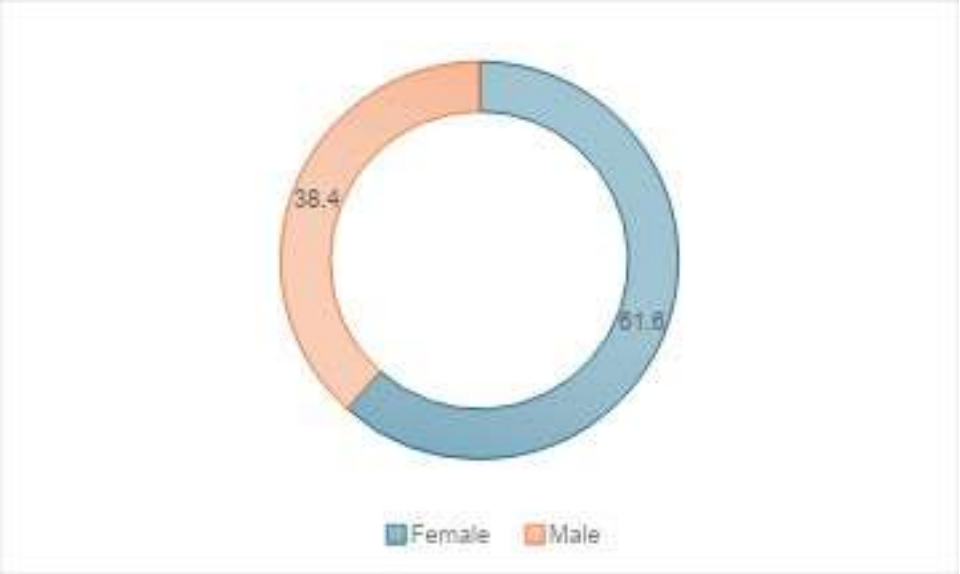

Figure 2: Distribution of Patients, by Gender

Table 3: Distribution of Patients, by History of Rheumatic Fever

		Number N = 216	Percentage (%)
History of Rheumatic Fever	Present	200	92.6
	Absent	16	7.4

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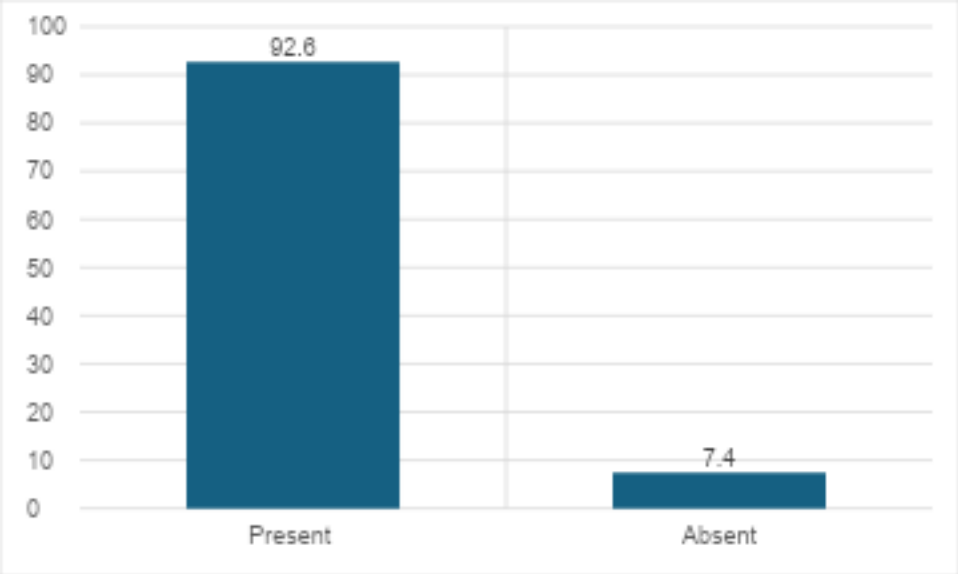

Figure 3: Distribution of Patients, by History of Rheumatic Fever

Table 4: Distribution of Patients, by Presence or Absence of Stenosis and Valvular Involvement

		Number N = 216	Percentage (%)

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Stenosis	Present	200	92.6
	Absent	16	7.4
Tricuspid stenosis	Present	1	0.5
	Absent	215	99.5
Mitral stenosis	Present	195	90.3
	Absent	21	9.7
Aortic stenosis	Present	22	10.2
	Absent	194	89.8

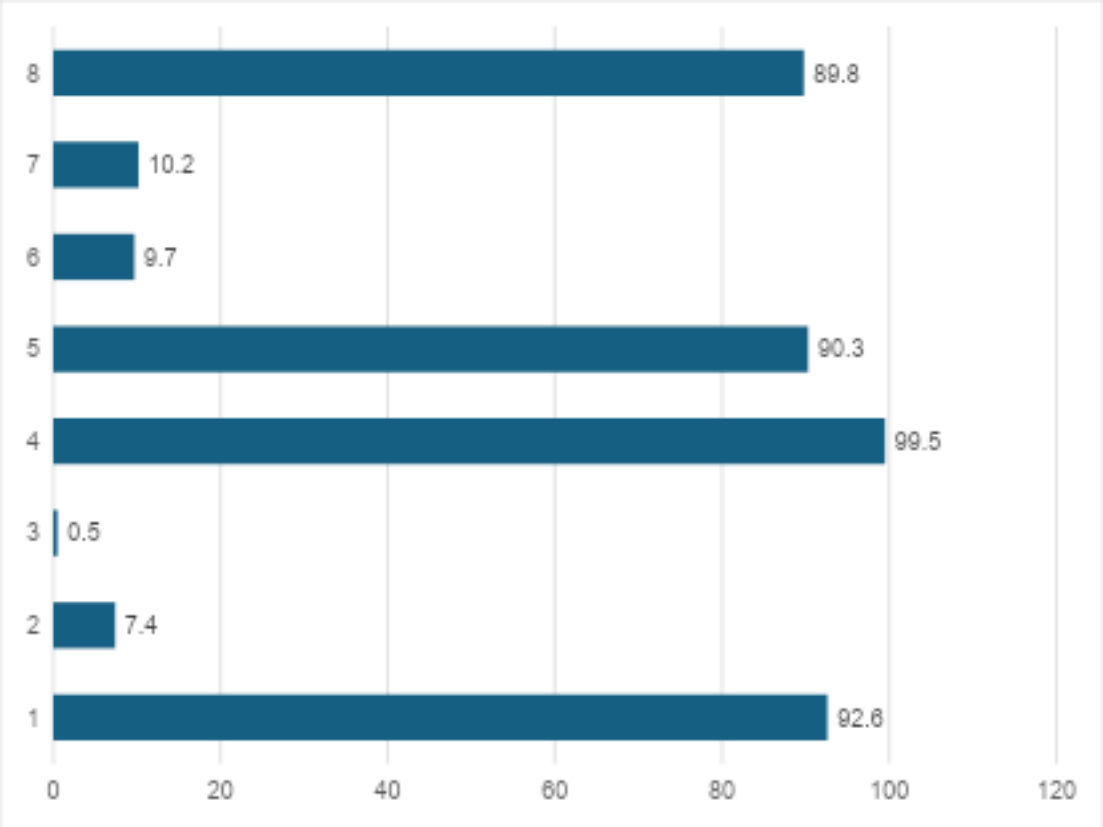

Figure 4: Distribution of Patients, by Presence or Absence of Stenosis and Valvular Involvement

Table 5: Distribution of Patients, by Presence or Absence of Regurgitation and Valvular Involvement

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		Number N = 216	Percentage (%)
Regurgitation	Present	214	99.1
	Absent	2	0.9
Tricuspid regurgitation	Present	1	0.5
	Absent	215	99.5
Mitral regurgitation	Present	210	97.2
	Absent	6	2.8
Aortic regurgitation	Present	157	72.7
	Absent	59	27.3

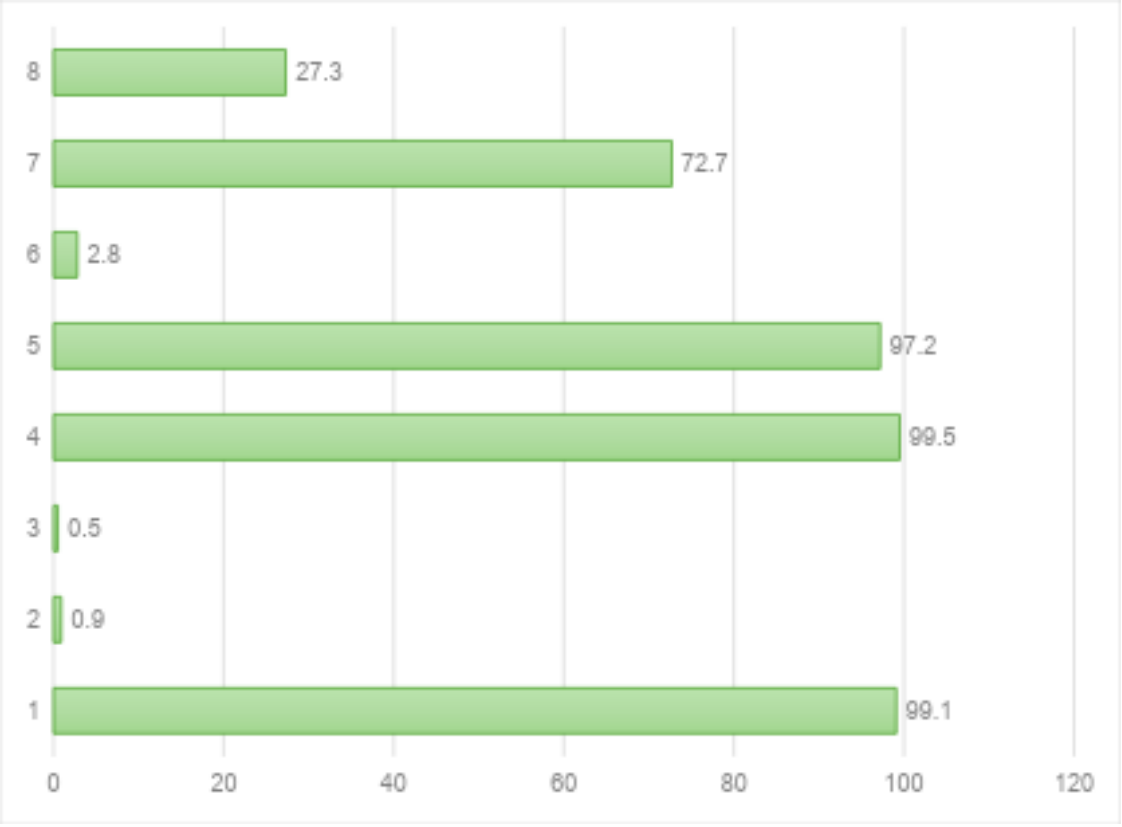

Figure 5: Distribution of Patients, by Presence or Absence of Regurgitation and Valvular Involvement

Table 6: Distribution of Patients, by Severity of Mitral Regurgitation

		Number N = 216	Percentage (%)
	Trivial	9	4.2
	Mild	131	60.6

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Mitral regurgitation	Moderate	59	27.3
	Severe	11	5.1
	Absent	6	2.8

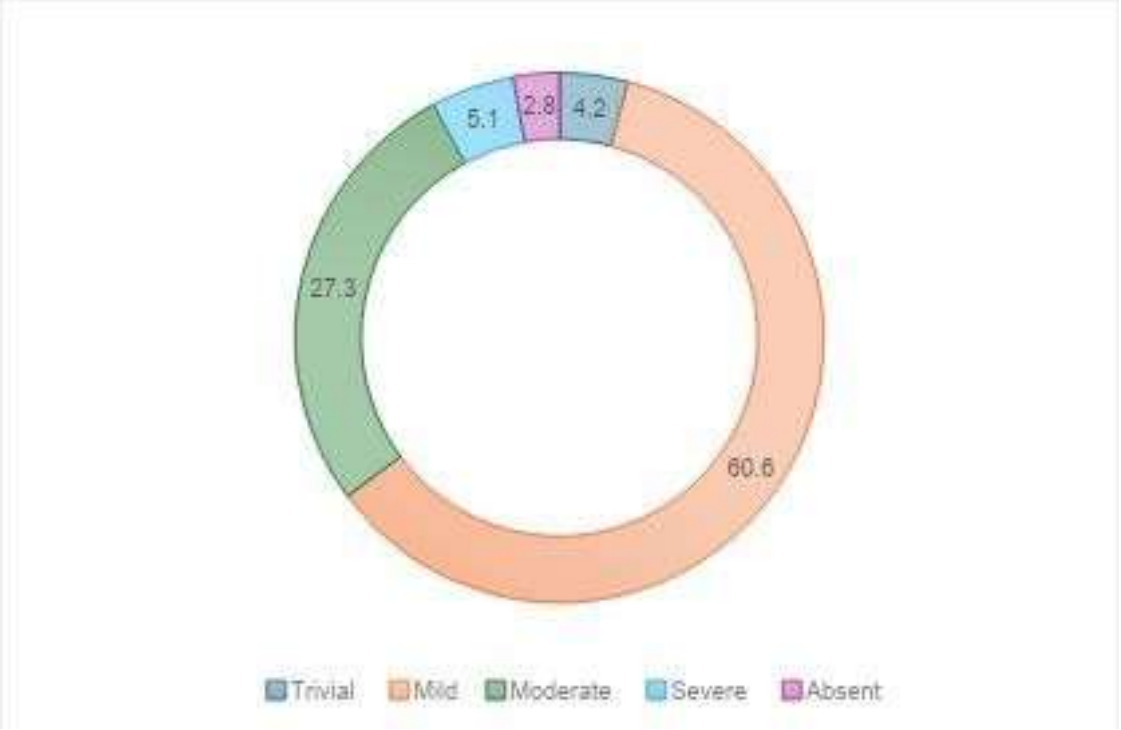

Figure 6: Distribution of Patients, by Severity of Mitral Regurgitation

Table 7: Distribution of Patients, by Severity of Aortic Regurgitation

		Number N = 216	**Percentage (%)**
Aortic regurgitation	Trivial	66	30.6
	Mild	91	42.1
	Absent	59	27.3

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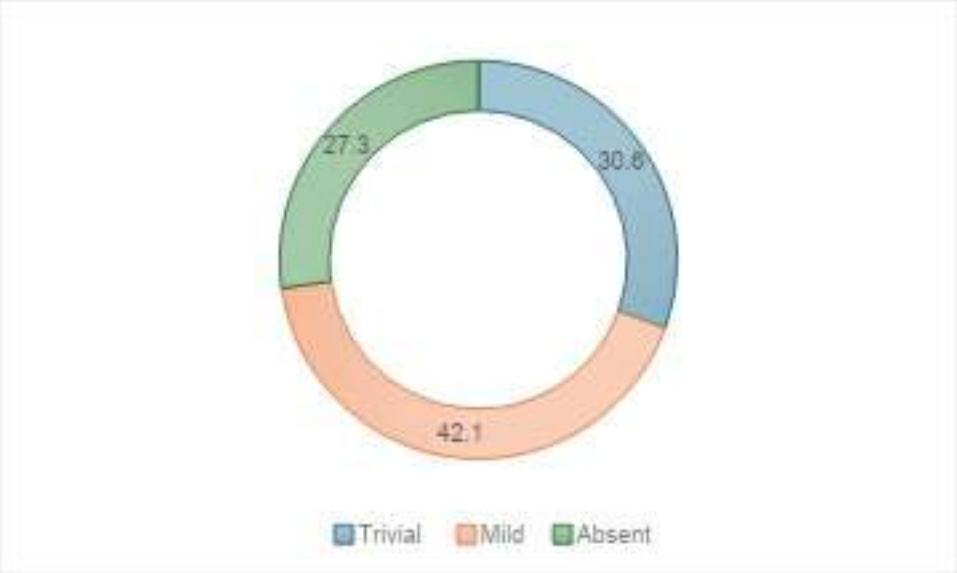

Figure 7: Distribution of Patients, by Severity of Aortic Regurgitation

2.0 Role of HLA-DRB1*0401 Allele

Among 40 patients, 25% were positive for HLA-DRB1*0401 (Table 8, Figure 8). Positive patients: 50% male, 50% female; 60% preoperative, 40% postoperative (Table 9, Figure 9). Gene expression higher in >40 years (mean 2.77 ± 0.54 vs. 1.97 ± 0.71; p=0.002; Table 10, Figure 10). No significant gender difference (female: 2.30 ± 0.75 vs. male: 2.22 ± 0.82; p=0.612; Table 11, Figure 11). Postoperative expression higher (2.80 ± 0.60 vs. 1.90 ± 0.62; p=0.001; Table 12, Figure 12).

Table 8: Distribution of Patients, by Results of Genetic Analysis

		Number (N = 40)	Percentage (%)
Gene expression	Positive	10	25.0
	Negative	30	75.0

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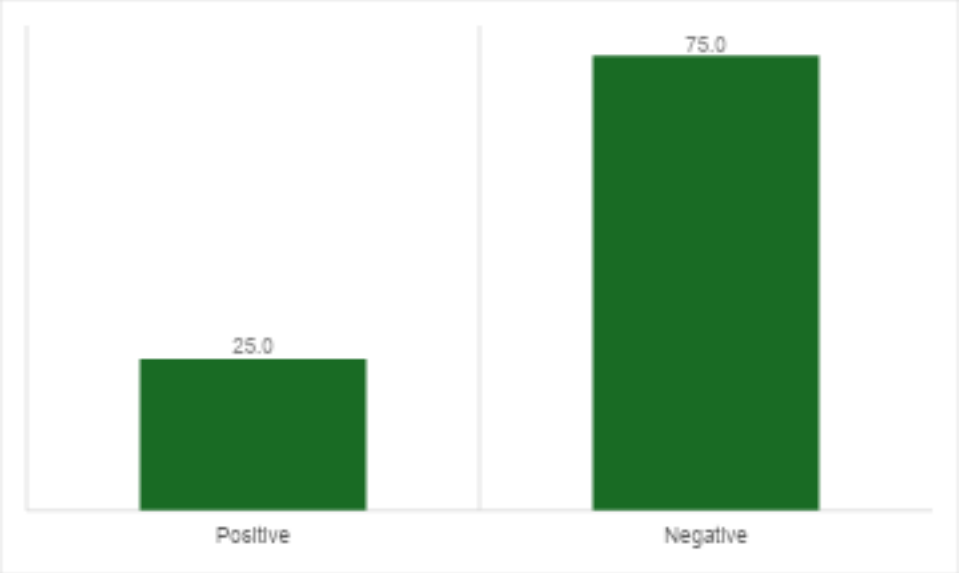

Figure 8: Distribution of Patients, by Results of Genetic Analysis

Table 9: Characteristics of Patients Found Positive in Genetic Analysis

		Number (N = 10)	**Percentage (%)**
Gender	Male	5	50.0
	Female	5	50.0
Status	Preoperative	6	60.0
	Postoperative	4	40.0

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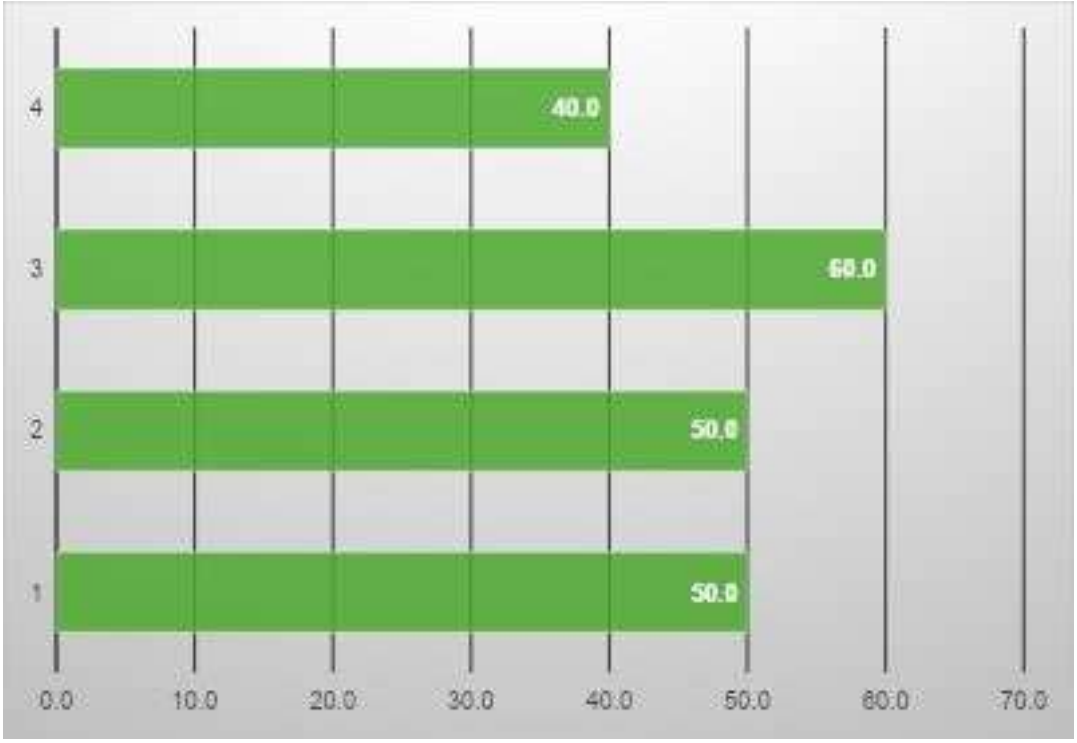

Figure 9: Characteristics of Patients Found Positive in Genetic Analysis

Table 10: Levels of Gene Expression, by Age of the Patients

Gene expression			
	Mean	**SD**	**P value**
Less than or equal to 40 years	1.97	0.71	0.002
More than 40 years	2.77	0.54	
The difference was statistically significant ($p<0.05$)			

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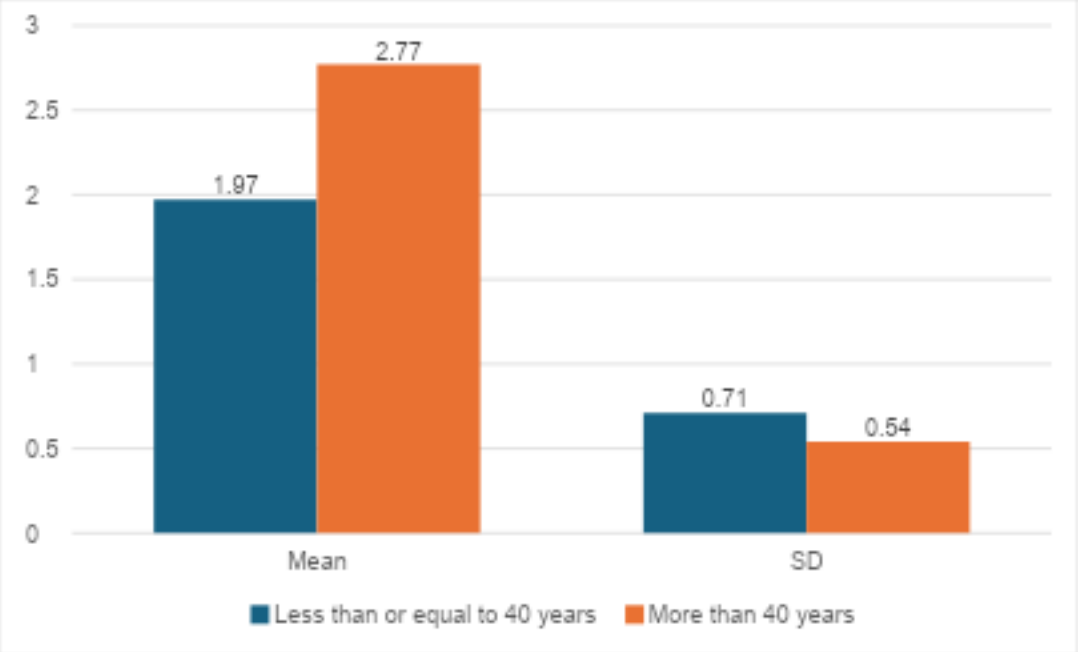

Figure 10: Levels of Gene Expression, by Age of the Patients

Table 11: Levels of Gene Expression, by Patient Gender

Gene expression			
	Mean	**SD**	**P value**
Male	2.22	0.82	0.612
Female	2.30	0.75	
The difference was not statistically important(p>0.05)			

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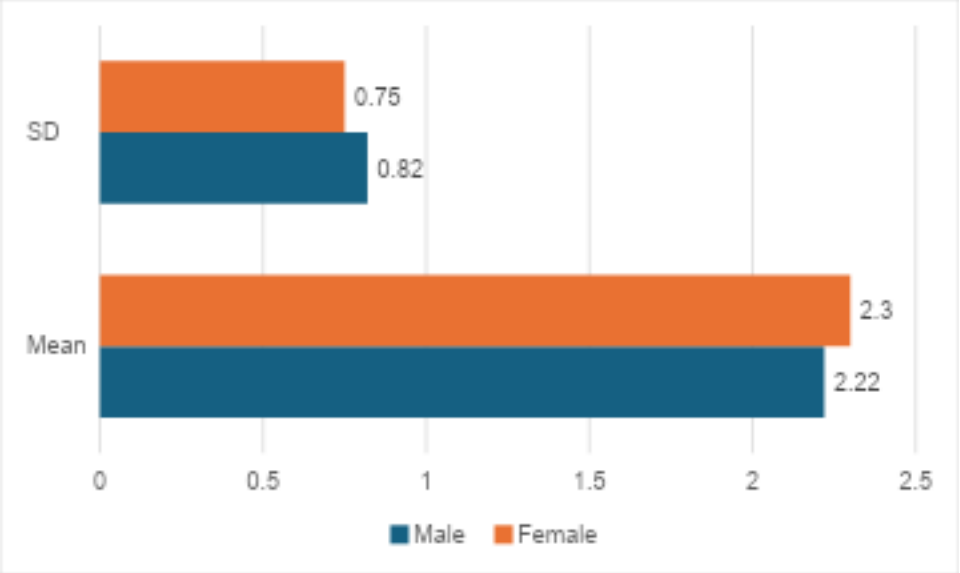

Figure 11: Levels of Gene Expression, by Patient Gender

Table 12: Levels of Gene Expression, by Operative Status

Gene expression			
	Mean	**SD**	**P value**
Preoperative	1.90	0.62	0.001
Postoperative	2.80	0.60	
The difference was statistically significant ($p<0.05$)			

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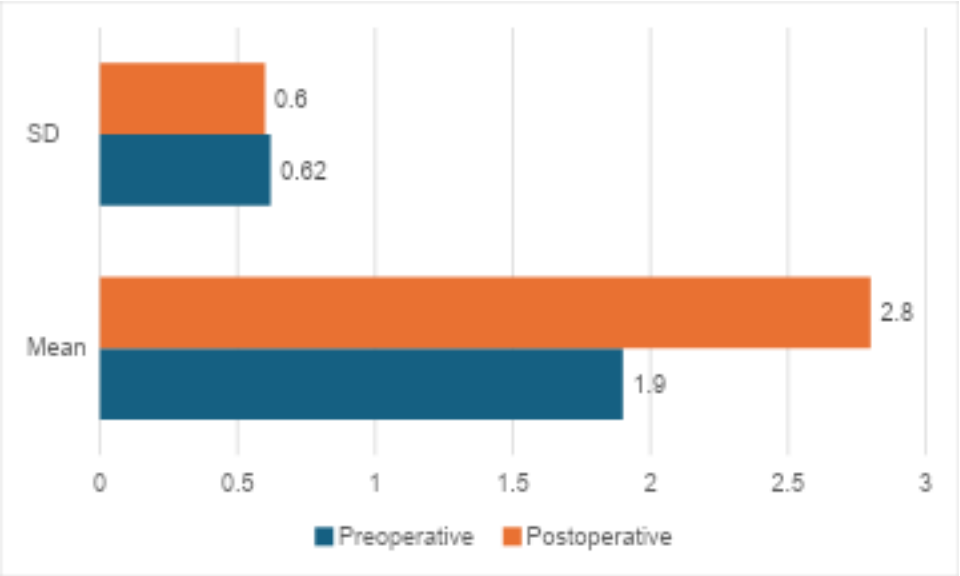

Figure 12: Levels of Gene Expression, by Operative Status

3.0 Role of Novel Biomarkers

Mean age: 47.5 ± 15.9 years. Males: 57.4%, females: 42.6% (Table 13, Figure 13). Preoperative: 45.4%, postoperative: 54.6% (Table 19, Figure 24). CRP mean: 4.5 ± 4.0 mg/L; 64.8% ≤5 mg/L (Table 14, Figure 14). Postoperative CRP higher (p=0.001; Table 15, Figure 15). IL-6 mean: 17.5 ± 20.8 pg/mL; 33.3% ≤7 pg/mL (Table 16, Figure 16). Postoperative IL-6 higher (p=0.002; Table 17, Figure 17). Troponin I positive: 12.0% (Table 18, Figure 18). No significant operative difference (p=0.594; Table 19, Figure 19). NT-proBNP positive: 10.2% (Table 20, Figure 20). No significant operative difference (p=0.203; Table 21, Figure 22).

Table 13: Distribution of Patients, by Gender

		Number N = 108	**Percentage (%)**
Gender	Female	46	42.6
	Male	62	57.4

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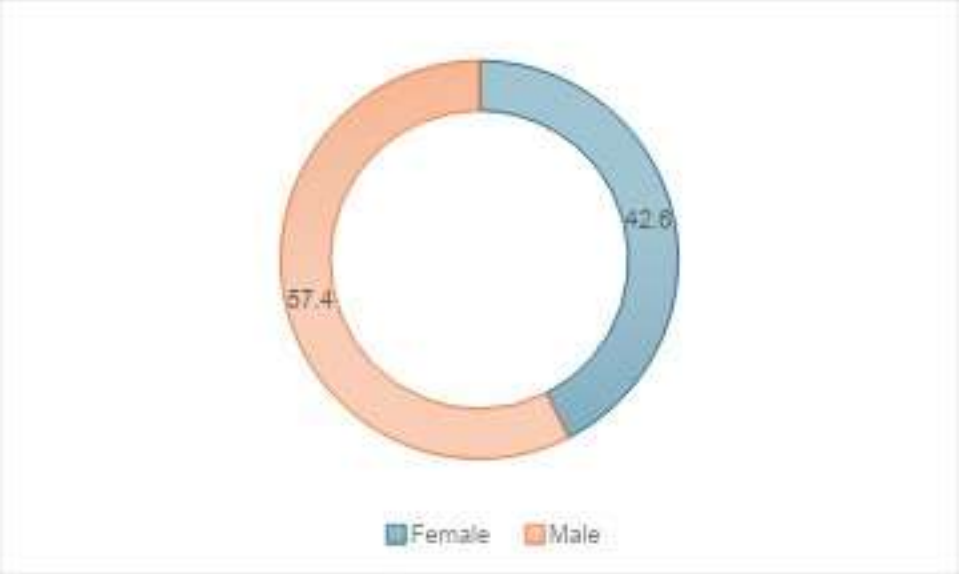

Figure 13: Distribution of Patients, by Gender

Table 14: Distribution of Patients, by Levels of C-Reactive Protein

		Number N = 108	**Percentage (%)**
C-reactive protein	Mean (SD)	4.5 (4.0)	
	Median (IQR)	2.7 (1.3 to 8.7)	
C-reactive protein	≤5	70	64.8
	>5	38	35.2

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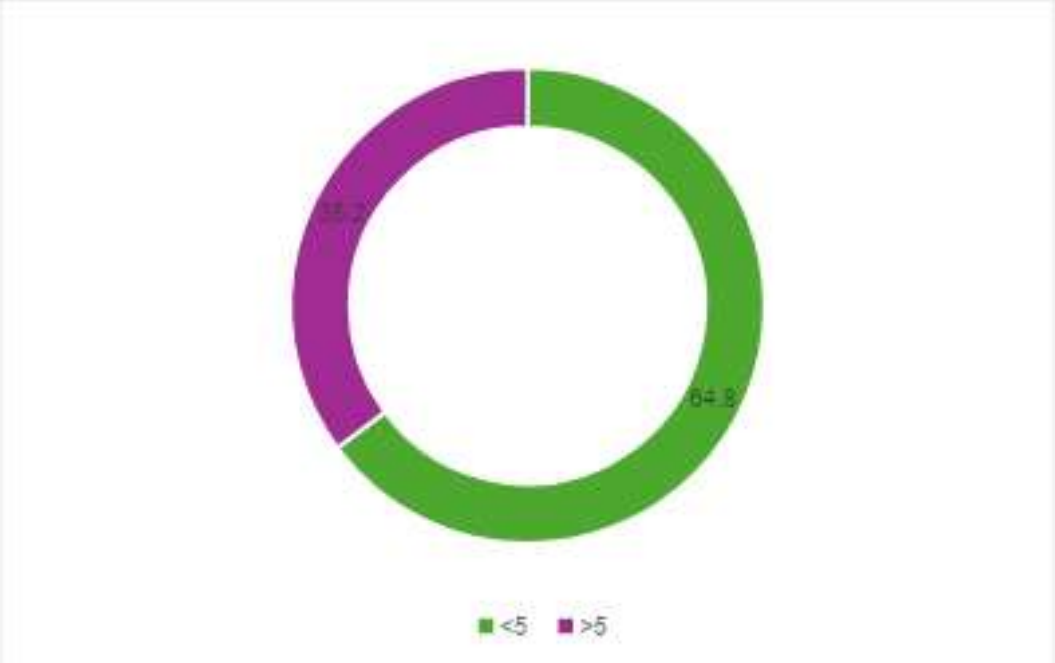

Figure 14: Distribution of Patients, by Levels of C-Reactive Protein

Table 15: Association Between Operative Status and Levels of C-Reactive Protein

		CRP		Total N = 108	P value
		≤5 N = 70	>5 N = 38		
		n (%)	n (%)	n (%)	
Status	Postop	40 (57.1)	9 (23.7)	49 (45.4)	0.001*
	preop	30 (42.9)	29 (76.3)	59 (54.6)	
*Statistically significant at p<0.05					

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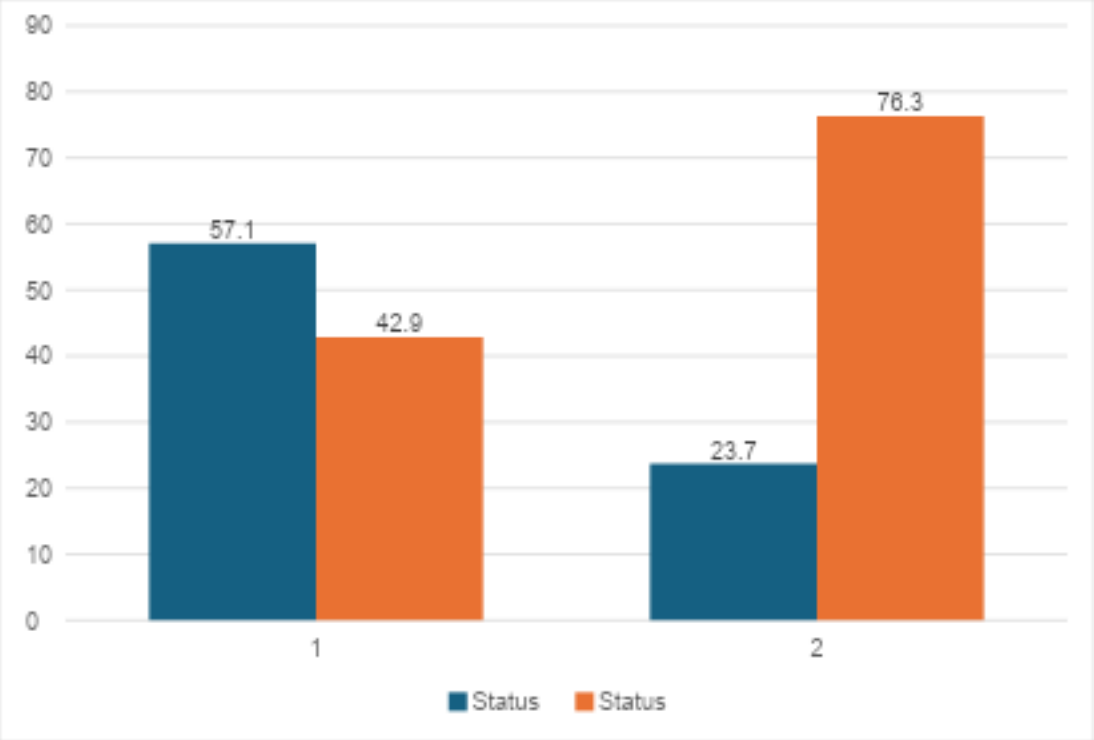

Figure 15*: Association Between Operative Status and Levels of C-Reactive Protein*

Table 16: Distribution of Patients, by Levels of Interleukin 6

		Number N = 108	**Percentage (%)**
Interleukin 6	Mean (SD)	17.5 (20.8)	
	Median (IQR)	10.0 (7.0 to 16.0)	
Interleukin 6	≤7	36	33.3
	>7	72	66.7

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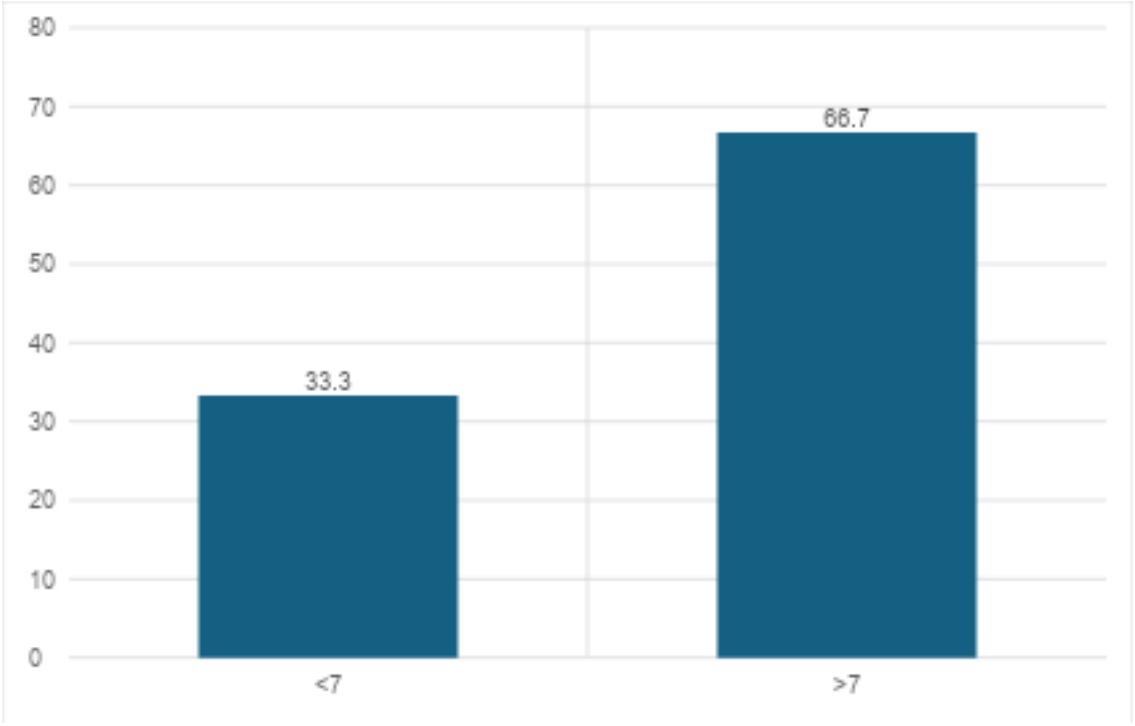

Figure 16: Distribution of Patients, by Levels of Interleukin 6

Table 17: Association Between Operative Status and Levels of Interleukin 6

		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					

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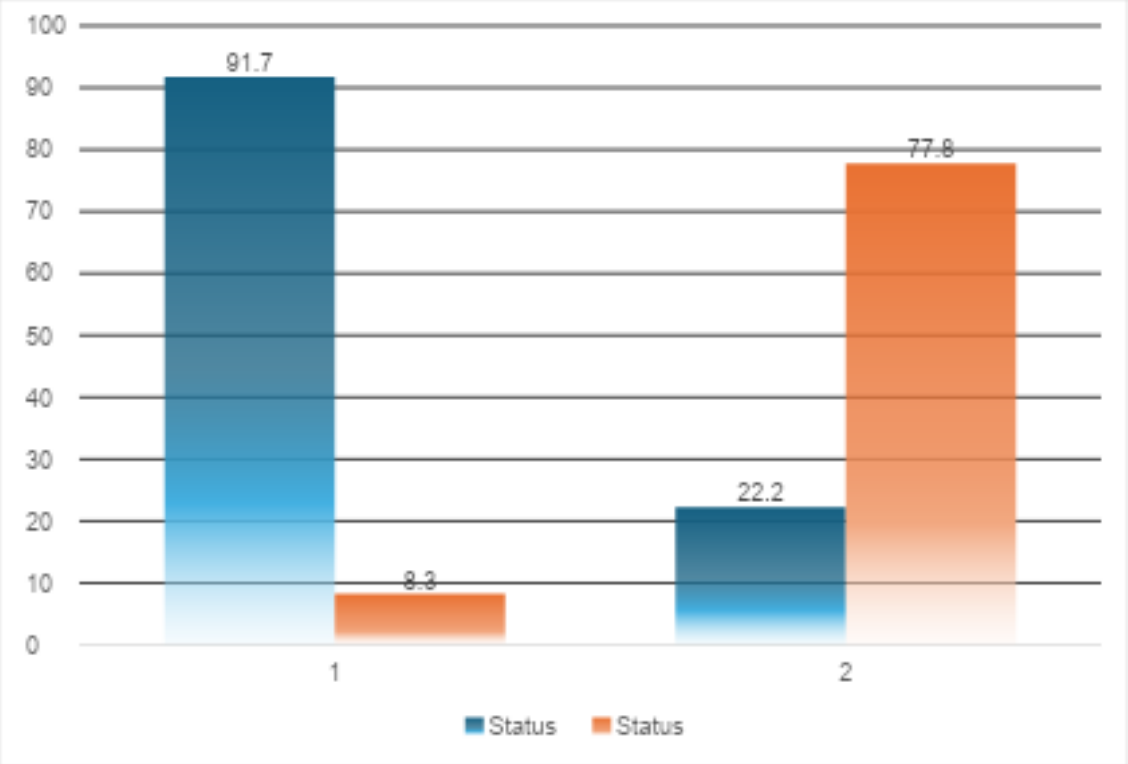

Figure 17: Association Between Operative Status and Levels of Interleukin 6

Table 18: Distribution of Patients, by Levels of Troponin I

		Number N = 108	**Percentage (%)**
Troponin I	Mean (SD)	9.9 (13.6)	
	Median (IQR)	6.2 (3.0 to 12.0)	
Troponin I	Negative	95	88.0
	Positive	13	12.0

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Figure 18: Distribution of Patients, by Levels of Troponin I

Table 19: 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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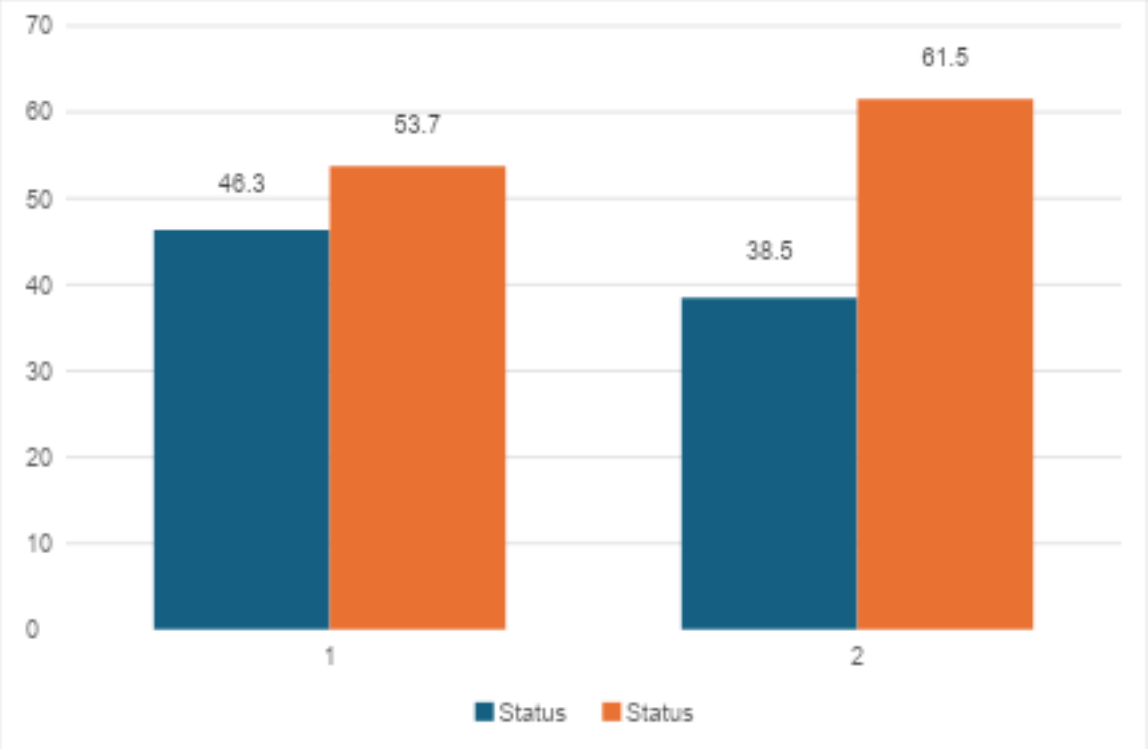

Figure 19: Association Between Operative Status and Levels of Troponin I

Table 20: 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

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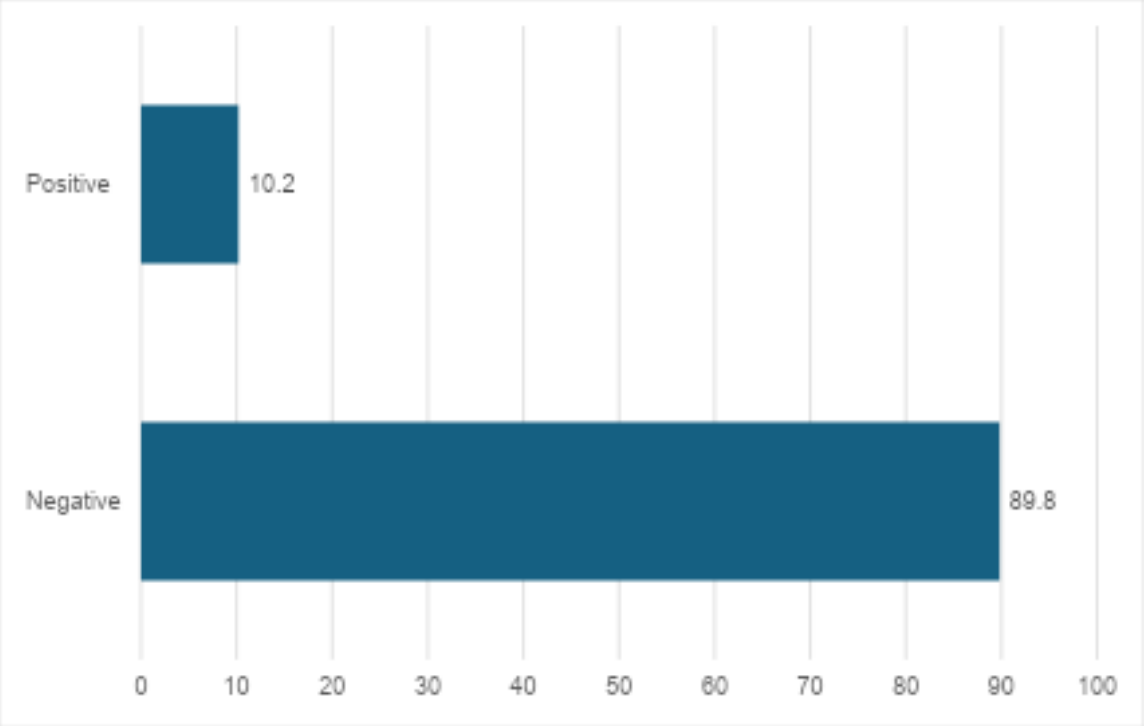

Figure 20: Distribution of Patients, by Levels of NTproBNP

Table 21: Association Between Operative Status and Levels of NTproBNP

		NTproBNP		Total N = 108	P value
		Negative N = 97	Positive N = 11		
		n (%)	n (%)	n (%)	
Status	Preop	46 (47.4)	3 (27.3)	49 (45.4)	0.203
	Postop	51 (52.6)	8 (72.7)	59 (54.6)	
*Statistically significant at p<0.05					

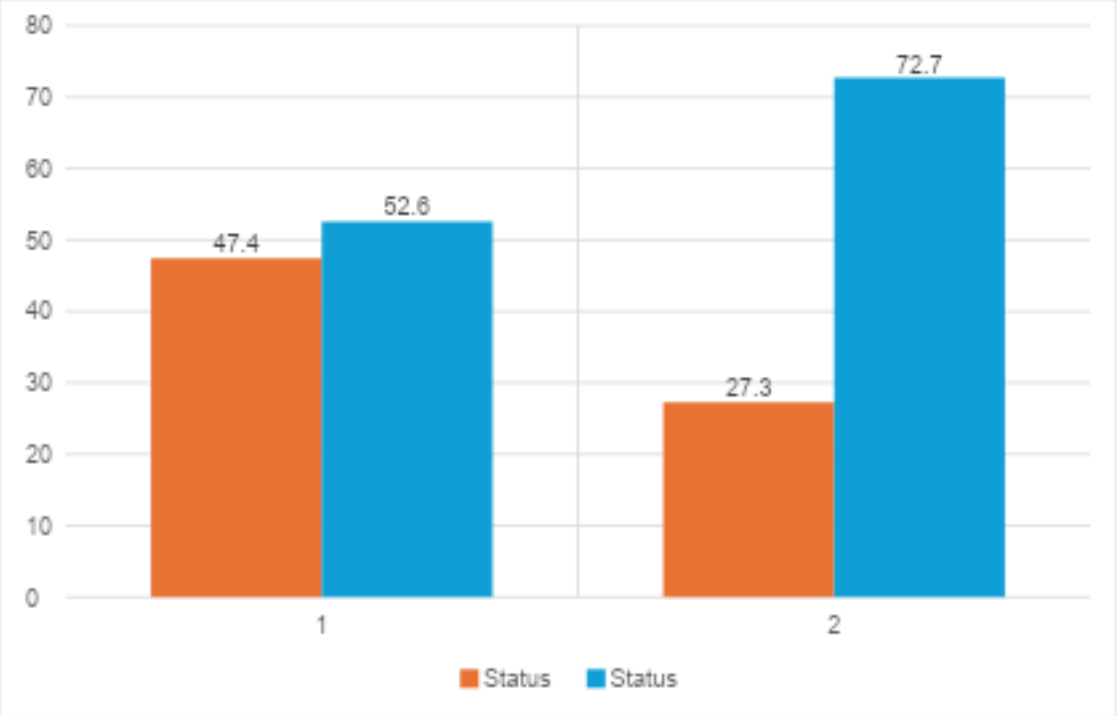

Figure 22: Association between Operative Status and Levels of NTproBNP

Discussion

The thesis findings align with global RHD data, emphasizing mitral dominance and biomarker utility postoperatively. The mean age of 43.7 years corresponds with RHD's chronic nature, peaking in middle age (Kumar & Tandon, 2013; Marijon et al., 2012). Females (61.6%) predominated, reflecting biological and socio-cultural factors (Guilherme & Kalil, 2010). A 92.6% RF history underscores ARF-RHD progression (Carapetis et al., 2016). Mitral stenosis (90.3%) and regurgitation (97.2%) dominated, consistent with valve susceptibility to autoimmune damage (Reményi et al., 2012).

Genetic analysis revealed 25% HLA-DRB1*0401 positivity, supporting susceptibility (Guilherme et al., 2000). Higher expression in postoperative ($p=0.001$) and older patients ($p=0.002$) indicates age and surgical influences (Stanevicha et al., 2003; Wade et al., 2019). No gender difference ($p=0.612$) aligns with neutral genetic associations (Zhou et al., 2019).

Biomarkers showed postoperative CRP and IL-6 elevation ($p<0.05$), indicating inflammation (Pepys & Hirschfield, 2003; Mihara et al., 2012). Stable troponin I and NT-proBNP ($p>0.05$) suggest limited perioperative utility (Keller et al., 2009; Januzzi et al., 2006).

Limitations: Single-center data; need for multi-ethnic studies. Future directions: Personalized medicine via genetics and AI-driven biomarker analysis.

Conclusion

RHD demands multidisciplinary strategies for prevention and management. Advances in genetics and biomarkers promise better outcomes, but global disparities persist. Research should prioritize affordable diagnostics and vaccines.

Comparative Perspectives

Our findings are consistent with global epidemiological data, which suggest that although the incidence of acute rheumatic fever is declining, the chronic burden of RHD remains

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disproportionately high in LMICs (GBD, 2017). Moreover, the predominance of mitral valve disease reflects patterns seen in African and South Asian populations (Zühlke et al., 2017). The demonstration of genetic and biomarker associations provides novel insights into disease pathogenesis and supports earlier recommendations for integrating molecular and serological diagnostics in routine clinical care.

Limitations

The study employed convenience sampling, which may limit generalizability. Additionally, biomarker levels may have been influenced by comorbid conditions not fully accounted for. Future multicentric, longitudinal studies are warranted to validate the prognostic value of these genetic and biomarker associations.

Recommendation

The present investigation sought to provide a comprehensive perspective on rheumatic heart disease (RHD) by examining patient demographics, genetic predispositions, and biomarker profiles. Each objective addressed within this study contributes valuable insights into distinct aspects of RHD pathophysiology and clinical management. To begin with, the descriptive evaluation of valvular abnormalities revealed clear trends in demographic distribution and disease characteristics. Most patients were identified as belonging to the middle-aged group, with females accounting for a considerable proportion. The mitral valve was the most frequently affected, predominantly through stenosis and regurgitation, emphasizing both the chronic progression and complex nature of RHD. These observations reinforce the urgent requirement for therapeutic interventions tailored to the specific valvular manifestations commonly encountered in this population.

The second focus of the study examined the role of the HLA-DRB1*0401 allele in determining genetic susceptibility to RHD. Approximately one-quarter of the participants were carriers of this allele, suggesting a possible genetic predisposition to the condition. Moreover, gene expression patterns associated with this allele were found to be significantly influenced by both patient age and surgical status, demonstrating the interaction between genetic background and clinical outcomes. These findings highlight the importance of incorporating genetic screening to identify vulnerable groups and to develop individualized treatment strategies.

A third component of the investigation assessed the diagnostic value of emerging biomarkers in RHD, specifically CRP, IL-6, troponin I, and NT-proBNP. Elevated concentrations of CRP and IL-6 were observed in postoperative individuals, indicating their potential use as indicators for monitoring inflammation and recovery following surgery. Conversely, troponin I and NT-proBNP levels showed no notable differences between preoperative and postoperative patients, implying their limited effectiveness in distinguishing surgical status in RHD. These outcomes underscore the necessity of carefully selecting and interpreting biomarkers in clinical contexts to ensure optimal patient management and improved prognostic outcomes.

In summary, this research offers a multidimensional understanding of RHD by integrating demographic analysis, genetic association studies, and biomarker evaluations. The results contribute meaningfully to advancing diagnostic, therapeutic, and management approaches for patients suffering from this condition. Future investigations should emphasize validating these findings in larger study populations, exploring additional biomarker candidates, and developing precision medicine strategies informed by genetic and biomarker profiles. By strengthening our knowledge base through such comprehensive research, patient care and long-term outcomes in RHD can be significantly enhanced.

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