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Original Article

Internal Medicine Section

Potential Role of NT-proBNP and Tissue Doppler Indices to Assess the Severity of Rheumatic Heart Disease: A Cross-sectional Study

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ABSTRACT

Introduction: Rheumatic Heart Disease (RHD) remains the primary cause of acquired Valvular Heart Disease (VHD) in developing countries. The role of Tissue Doppler Indices (TDI) in RHD is understudied. This study aims to fill evidence gaps identified by the American College of Cardiology/American Heart Association in the management of Valvular Heart Disease (VHD) by analysing newer echocardiographic techniques {Tissue Doppler Imaging (TDI)} and biochemical markers (NT-proBNP) against clinical parameters {New York Heart Association (NYHA)} in an understudied patient group.

Aim: To evaluate the role of TDI and its association with the functional class of dyspnoea and serum NT-proBNP levels in RHD.

Materials and Methods: This cross-sectional study was conducted in the Cardiology and Medicine departments, Central Gujarat, Western India, from January 2021 to June 2022. Fifty-seven consenting adult patients with RHD who underwent echocardiography with Standard Echocardiographic Techniques (SET) to stratify VHD severity were included. Patients were divided into three sub-groups: a) Isolated MR and MR with mild/moderate MS (n=23); b) Isolated MS and MS with mild MR (n=29); and c) Isolated MS and MS with mild or moderate MR (n=48). TDI parameters (e', a', e'/a', and E/e') at medial mitral, lateral mitral, and tricuspid annuli, NYHA classification, and serum NT-proBNP levels were analysed. The Analysis of Variance (ANOVA) was used to assess the association between NYHA class and clinical and NT-proBNP parameters. The Pearson correlation coefficient was employed to determine linear relationships between NT-proBNP and TDI parameters.

Results: The mean age was 45.4±16 years, with the age groups 20-40 years (n=20) and 40-60 years (n=22) having a nearly equal distribution. The female-to-male ratio was 1.48 (34/23). In subgroup C, the a' velocity decreased from 13.74±3.92 cm/s in NYHA I to 5.17±1.98 cm/s in NYHA IV (p=0.0312), and the e'/a' ratio increased from 0.96±0.40 in NYHA I to 2.41±1.00 in NYHA IV (p=0.0210). These changes paralleled trends in a' value (p=0.0306) and e'/a' ratio (p=0.0157) with increasing NT-proBNP levels.

Conclusion: At the tricuspid annulus, the e'/a' ratio and a' velocity can complement NT-proBNP in cases where there is a discrepancy between the clinical status of the patient and the severity of the valve lesion as determined by SET. Larger-scale studies are needed to further evaluate the association between TDI parameters and long-term clinical outcomes, as well as to identify the optimal timing for surgical intervention in RHD patients.

Keywords: Natriuretic peptides, Tissue doppler, Valvular heart disease

INTRODUCTION

Primary Valvular Heart Disease (VHD), though less common than Ischaemic Heart Diseases (IHD), hypertension, stroke, and diabetes mellitus, leads to significant morbidity and often premature mortality [1]. Acute Rheumatic Fever (ARF) resulting in Rheumatic Heart Disease (RHD) remains the major cause of acquired VHD in low- and middle-income countries [2]. The Mitral Valve (MV) is almost invariably involved [2], with Mitral Regurgitation (MR) being the most frequent valvular lesion [3], and isolated aortic valve lesions being uncommon [2,3]. Mitral Stenosis (MS), which tends to manifest later, shares morphological characteristics with MR [3]. Approximately 27% of RHD patients develop Heart Failure (HF) within five years [4], necessitating interventional management for those with symptomatic and severe chronic valvular lesions [5]. The survival post-interventional procedure is inversely related to the New York Heart Association (NYHA) [6] class of complaints of the patients [5,7].

The progression of HF in VHD patients is less precisely determined by lesions that are themselves influenced by afterload [8-10] and preload [11]. Therefore, in preload-dependent lesions such as MS [12], and afterload-dependent lesions like Aortic Stenosis (AS) [8-10], flow parameters assessed by SET, including valve area planimetry and Doppler velocities like early inflow velocity by pulse wave Doppler (E), may not be accurate.

The TDI derived parameters, such as early annular velocity (e') and diastasis annular velocity (a'), are used to evaluate the presence and severity of diastolic dysfunction [12]. The E/e' ratio, being un-affected by Left Ventricular (LV) systolic dysfunction, is independent of preload and afterload [12], making it a more reliable measure in such cases of VHD.

The functional status of the Right Ventricle (RV) is a key determinant of clinical symptoms, exercise capacity, pre-operative survival, and post-operative outcomes in patients with MS. Some patients with moderate to severe MS and a normal RV ejection fraction may be symptomatic, while others remain asymptomatic, even with similar valve areas [13], indicating that SET may not always correlate with the clinical status of these patients.

Natriuretic peptides, released by atrial walls in response to stretch stimuli, represent one of the earliest adaptive responses to volume overload. NT-proBNP levels are indicative of MS severity [14] and can be associated with subclinical systolic dysfunction measured by LV-TDI [15,16]. NT-proBNP is also effective in patients with significant structural heart diseases even in the presence of Atrial Fibrillation (AF) [17]. Elevated NT-proBNP levels are associated with higher mortality and morbidity in patients with chronic stable HF [18].

Thus, this study was undertaken to determine whether TDI parameters correlate with the NYHA class of dyspnoea and/or NT-proBNP levels in patients with RHD.

MATERIALS AND METHODS

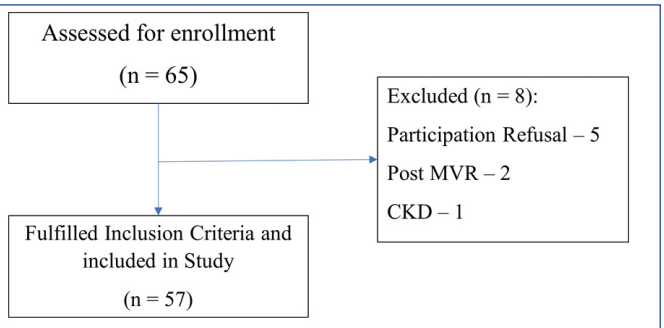
This cross-sectional study was conducted at the Cardiology and Medicine departments of a tertiary care teaching hospital located in central Gujarat, Western India, from January 2021 to June 2022. Approval was obtained from the Institutional Ethical Committee (IEC/BU/127/Faculty/16/7512021).

Sample size calculation: The prevalence of RHD in South Gujarat in 2017 was reported as 9.2 per 1000 population [19]. The sample size for this cross-sectional study was calculated using the formula $4pq/d^2$, where p=0.92, q=99.08, and d=3 (97% Confidence Interval). The resulting sample size was 40.5. Anticipating a dropout rate of 10%, the final sample size was adjusted to 44.5, which was then rounded up to 45.

Inclusion criteria: A total of 57 adult patients with native valve RHD, either previously known or newly diagnosed, and irrespective of medication status, were included in the study.

Exclusion criteria: Patients with Chronic Kidney Disease (CKD) (n=1) and those who had undergone valve replacement surgeries (n=2, MV Replacement surgery) were excluded from the study.

The selection of study participants according to inclusion and exclusion criteria are mentioned in [Table/Fig-1].



[Table/Fig-1]: Study flowchart.

Procedure

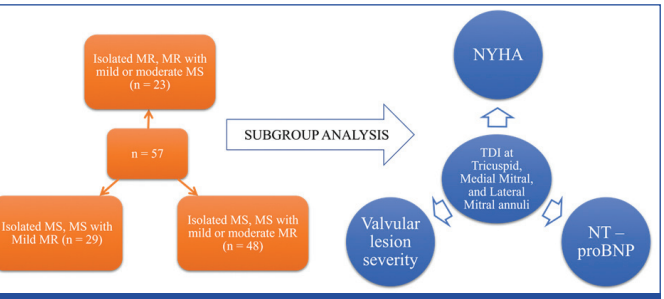
NYHA class of dyspnoea was assessed for all patients. Echocardiographic evaluation and grading of the severity of valvular involvement into mild, moderate, or severe categories were performed according to the World Heart Federation (WHF) guidelines [20].

Multivalvular Diseases (MVD) are clinically prevalent, with RHD being the most common aetiology of MVD [21]. To allow for a more clinically relevant classification, the patients were divided into three sub-groups [Table/Fig-2,3]:

a) Isolated MR, or MR with coexistent mild or moderate MS (n=23) {Red Box in [Table/Fig-3]};

b) Isolated MS, or MS with Mild MR (n=29) {Black Box in [Table/Fig-3]};

c) Isolated MS or MS with mild or moderate MR (n=48) {Green Box in [Table/Fig-3]}. Each sub-group was evaluated using TDI, NT-proBNP levels, and the NYHA class of dyspnoea.



[Table/Fig-2]: Study design.

	No MS	Mild MS	Moderate MS	Severe MS	Total
No MR	0	0	1	10	11
Mild MR	0	2	3	13	18
Moderate MR	1	1	8	10	20
Severe MR	5	2	1	0	8
Total	6	5	13	33	57

[Table/Fig-3]: Frequency distribution and subgrouping of the patients as per the Echocardiography lesions.

However, four RHD patients could not undergo TDI evaluation as they passed away in critical care before TDI or NT-proBNP measurements could be performed. TDI parameters (Early ventricular filling velocity [E], early annular velocity [e'], diastasis ventricular filling velocity [a'], and peak systolic velocity [Sm]) were measured by pulsed wave Doppler at the medial mitral, lateral mitral, and tricuspid annuli. The e'/a' ratio was calculated for each site. The TDI parameters were analysed in relation to the NYHA class of dyspnoea and serum NT-proBNP levels within each sub-group.

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel 2016 and analysed using Stata 14.2 statistical software. Descriptive statistics such as mean (SD), median (IQR), and frequency (%) were calculated to describe the demographic, clinical, biochemical, and radiological characteristics of the study population. Analysis of Variance (ANOVA) was employed to determine the association between NYHA functional class and the clinical and serum N-terminal pro b-type natriuretic peptide (NT-proBNP) parameters. The Pearson correlation coefficient was used to assess linear relationships between NT-proBNP and continuous variables, like TDI parameters.

RESULTS

This study included a total of 57 patients with native valve RHD, with a mean age of 45.4 years. Out of these, four patients could not undergo TDI evaluation and NT-proBNP level assay. The majority of the participants were female (59.6%; n=34), and the most common age group was 41 to 60 years (38.60%, n=22). There were four patients from 18-20 years, 20 in the 21-40 years age group, and 11 above 60 years of age. On ECGs, 24 patients (42.1%) presented with Atrial Fibrillation (AF), with or without secondary conduction abnormalities.

Out of the 57 patients [Table/Fig-4], four were asymptomatic (NYHA Class I). The majority had Class III symptoms (n=25; 43.86%), followed by NYHA Class II symptoms (n=21; 36.84%). Seven patients experienced dyspnoea at rest, accounting for approximately 12.28%. Of these seven, four had severe MS and two had severe MR. Only two of these seven had severe Pulmonary Arterial Hypertension (PAH), both with AF.

Out of the 46 patients with some degree of MR, 19 (41.30%) had NYHA Class III symptoms. Similarly, out of the 51 patients with some degree of MS, 24 (47.06%) had Class III symptoms. No statistically significant association was found between the severity of MR (p=0.561) or MS (p=0.749) and the symptomatic state of the patient.

Since there are no established cut-offs for serum levels, the highest value of 35,000 pg/mL was excluded, and the remaining values were divided into four classes based on median and interquartile distribution. The classes (in pg/mL) were as follows: minimum value to 412.81; 412.81 to 1246; 1246 to 2300; and 2300 to maximum value. The mean NT-proBNP level was 3253.07 pg/mL (SD=6189.098 pg/mL). The highest level recorded was >35,000 pg/mL, and the lowest was

NYHA grading	MR					MS				
	No MR	Mild MR	Moderate MR	Severe MR	Total	No MS	Mild MS	Moderate MS	Severe MS	Total
I	0	2	2	0	4	0	0	2	2	4
II	5	7	5	4	21	4	1	4	12	21
III	6	6	11	2	25	1	3	6	15	25
IV	0	3	2	2	7	1	1	1	4	7
Total	11	18	20	8	57	6	5	13	33	57
p-value	0.561					0.749				

[Table/Fig-4]: Frequency table for severity of valvular lesion versus NYHA class of dyspnoea.
MR: Mitral regurgitation; MS: Mitral stenosis; NYHA: New York heart association

111.7 pg/mL. The mean levels according to the NYHA classifications were:

- NYHA I: 349.7 pg/mL (SD=157.57 pg/mL); n=3
- NYHA II: 682.0 pg/mL (SD=581.68 pg/mL); n=19
- NYHA III: 2024.96 pg/mL (SD=1487.84 pg/mL); n=24
- NYHA IV: 15686.57 pg/mL (SD=10532.32 pg/mL); n=7

When analysed against NYHA class [Table/Fig-5], NT-proBNP levels were found to increase significantly as the NYHA class of symptoms worsened (p<0.001).

NYHA grading		NT-proBNP Levels (in pg/mL)				Total
		Group-1 (111.7-412.80)	Group-2 (412.81-1246.00)	Group-3 (1246.01-2300.00)	Group-4 (2300.01->35000)	
I	n	2	1	0	0	3
	(%)	66.67	33.33	--	--	100.00
II	n	10	6	3	0	19
	(%)	52.63	31.58	15.79	--	100.00
III	n	2	6	10	6	24
	(%)	8.33	25.00	41.67	25.00	100.00
IV	n	0	0	0	7	7
	(%)	0.00	0.00	0.00	100.00	100.00
Total		14	13	13	13	53
		26.42	24.53	24.53	24.53	100.00

[Table/Fig-5]: NYHA grades vs. NT-proBNP groups frequency distribution chart.
p-value <0.001 (ANOVA test)

With NYHA [Table/Fig-6]: At both the medial and lateral mitral annulus, the a' velocity showed a decreasing trend, and the e'/a' ratio showed an increasing trend, neither of which were statistically significant when analysed against NYHA class of symptoms. However, at the tricuspid annulus, the a' velocity decreased from 13.25±0 cm/s to 3.85±0.75 cm/s (p=0.0361) and the e'/a' ratio increased from 0.74±0 to 3.09±0.47 (p=0.0054) as NYHA Class symptoms progressed from I to IV.

With NT-proBNP [Table/Fig-7]: The E/e' ratio showed a statistically significant regression as NT-proBNP levels increased (p<0.0001). The a' velocity at the tricuspid annulus had a negative regression (p=0.0217), and the e'/a' ratio had a positive regression (p=0.0098).

With NYHA [Table/Fig-6]: The TDI parameters showed no statistically significant changes at the medial or lateral mitral annuli.

NYHA class	Class-I (Mean±SD)	Class-II (Mean±SD)	Class-III (Mean±SD)	Class-IV (Mean±SD)	p-value
At the medial mitral annulus					
MR with No/Mild/Moderate MS:					
e' (in cm/s)	8.83±0.89	6.1±1.59	8.06±3.07	5.62±0.31	0.1985
a' (in cm/s)	13.35±0.15	7.75±2.09	9.50±3.17	9.74±2.34	0.0995
e'/a'	0.66±0.07	0.83±0.29	0.98±0.47	0.60±0.14	0.4226
E/e' (x10)	0.20±0.12	0.30±0.16	0.25±0.17	0.34±0.11	0.7238
Sm (in cm/s)	8.93±0.75	7.59±1.64	8.43±1.97	7.84±1.68	0.7082
MS with No/Mild MR:					
e' (in cm/s)	7.78±0	7.33±2.38	8.29±2.81	7.14±5.13	0.8559
a' (in cm/s)	11.57±0	8.98±4.84	9.43±4.11	6.57±0.88	0.6989
e'/a'	0.67±0	0.96±0.44	1.01±0.50	1.09±0.83	0.9005
E/e' (x10)	0.32±0	0.28±0.13	0.27±0.13	0.57±0.49	0.1142
Sm (in cm/s)	7.99±0	8.06±1.34	8.09±2.02	7.34±2.15	0.9263
MS with No/Mild/Moderate MR:					
e' (in cm/s)	8.48±0.87	7.12±2.55	7.81±2.71	7.48±3.66	0.8274
a' (in cm/s)	12.76±1.04	8.94±4.38	9.88±4.31	8.32±2.58	0.4428
e'/a'	0.66±0.05	0.90±0.41	0.97±0.53	0.95±0.62	0.7781
E/e' (x10)	0.24±0.11	0.30±0.14	0.29±0.13	0.45±0.38	0.2720
Sm (in cm/s)	8.62±0.76	8.13±1.87	8.06±1.75	7.42±1.76	0.8073
At the lateral mitral annulus					
MR with No/Mild/Moderate MS					
e' (in cm/s)	7.15±0.59	9.31±3.70	9.42±2.90	5.45±0.93	0.2208
a' (in cm/s)	7.25±2.82	7.60±1.86	9.93±4.99	7.23±3.92	0.5636
e'/a'	1.08±0.50	1.27±0.47	1.20±0.80	0.93±0.53	0.8995
E/e' (x10)	0.23±0.10	0.18±0.06	0.19±0.07	0.37±0.18	**0.0341**
Sm (in cm/s)	10.05±2.62	8.53±2.01	8.10±1.61	7.43±0.85	0.4297
MS with No/Mild MR					
e' (in cm/s)	8.62±0	7.38±2.43	9.13±2.19	8.42±5.47	0.5119
a' (in cm/s)	8.83±0	8.13±3.60	8.81±3.75	6.79±3.81	0.8551
e'/a'	0.98±0	1.03±0.46	1.22±0.57	1.44±0.86	0.6599
E/e' (x10)	0.29±0	0.29±0.18	0.24±0.12	0.40±0.20	0.4371
Sm (in cm/s)	11.99±0	7.96±1.29	8.38±1.45	7.95±1.53	0.0739
MS with No/Mild/Moderate MR					
e' (in cm/s)	7.64±0.95	7.61±2.25	8.44±2.41	7.91±3.93	0.7821
a' (in cm/s)	7.78±2.19	8.00±3.47	8.90±3.13	7.06±3.00	0.6244
e'/a'	1.05±0.36	1.07±0.43	1.13±0.68	1.28±0.68	0.9256
E/e' (x10)	0.25±0.77	0.28±0.16	0.26±0.12	0.36±0.16	0.5379
Sm (in cm/s)	10.70±2.16	8.51±2.45	8.17±1.31	8.05±1.18	0.1535
AT the tricuspid annulus					
MR with No/Mild/Moderate MS					
e' (in cm/s)	13.67±0.89	10.23±4.10	11.68±4.49	9.70±4.55	0.6828
a' (in cm/s)	13.98±5.51	14.11±4.23	15.72±6.60	7.68±5.00	0.2423
e'/a'	1.07±0.49	0.82±0.60	1.01±0.91	1.81±1.27	0.4262
E/e' (x10)	0.13±0.07	0.17±0.08	0.16±0.12	0.21±0.04	0.8369
Sm (in cm/s)	13.14±3.11	11.15±1.91	12.23±4.33	7.75±2.49	0.2361
MS with No/Mild MR					
e' (in cm/s)	9.88±0	9.70±2.24	12.27±4.87	12.11±4.13	0.4729
a' (in cm/s)	13.25±0	14.63±5.58	14.36±5.77	3.85±0.75	**0.0361**
e'/a'	0.74±0	0.88±0.70	1.11±1.00	3.09±0.47	**0.0054**
E/e' (x10)	0.25±0	0.18±0.05	0.20±0.17	0.24±0.08	0.9034
Sm (in cm/s)	10.72±0	10.57±1.25	11.35±3.19	7.99±2.33	0.2551
MS with No/Mild/Moderate MR					
e' (in cm/s)	12.40±2.28	10.05±3.27	12.19±3.92	11.18±3.19	0.3815

a' (in cm/s)	13.74±3.92	13.93±5.47	12.90±6.17	5.17±1.98	**0.0312**
e'/a'	0.96±0.40	0.94±0.72	1.29±0.95	2.41±1.00	**0.0210**
E/e' (x10)	0.17±0.09	0.19±0.06	0.19±0.13	0.23±0.06	0.8569
Sm (in cm/s)	12.33±2.61	10.76±1.60	10.81±2.98	8.58±2.27	0.2054

[Table/Fig-6]: Association of TDI parameters with functional NYHA.
a': Diastasis ventricular filling velocity; e': Early ventricular filling velocity; E: Rapid LV filling velocity; Sm: Peak atrial systolic velocity

At the tricuspid annulus, it was observed that as the NYHA class of symptoms worsened, the a' velocity decreased from 13.74±3.92 cm/s to 5.17±1.98 cm/s (p=0.0312) and the e'/a' ratio increased from 0.96±0.40 to 2.41±1.00 (p=0.0210).

With NT-proBNP [Table/Fig-7]: This trend of the TDI parameters with subjective worsening of NYHA was supported objectively by similar trends of these parameters with increasing NT-proBNP levels. At the tricuspid annulus, the a' velocity had a negative regression with NT-proBNP levels (p=0.0306), and the e'/a' ratio had a positive regression (p=0.0157), similar to the findings in subgroup B [Table/Fig-8]. The E/e' ratio showed a statistically significant regression as NT-proBNP levels increased (p=0.0001).

NT-proBNP levels	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
At the medial mitral annulus					
a. MR with No/Mild/Moderate MS:					
Regression	-0.2273	0.1668	-0.2523	0.1152	-0.1848
p-value	0.3217	0.4700	0.2699	0.6191	0.4225
b. MS with No/Mild MR:					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	-0.1916	-0.1646	-0.0743	0.7321	-0.3156
p-value	0.3383	0.4121	0.7128	**0.0001**	0.1089
c. MS with No/Mild/Moderate MR:					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	-0.1002	-0.0873	-0.0518	0.5356	-0.2785
p-value	0.5126	0.5687	0.7356	**0.0001**	0.0639
At the lateral mitral annulus					
a. MR with No/Mild/Moderate MS					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	-0.3440	0.1313	-0.3182	0.3456	-0.2226
p-value	0.1268	0.5706	0.1597	0.1249	0.3320
b. MS with No/Mild MR					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	-0.0571	0.1084	-0.0825	0.3274	0.1078
p-value	0.7773	0.5906	0.6823	0.0955	0.5927
c. MS with No/Mild/Moderate MR					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	-0.0695	0.0927	-0.0916	0.2641	0.0256
p-value	0.6500	0.5446	0.5497	0.0796	0.8673
At the tricuspid annulus					
a. MR with No/Mild/Moderate MS					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	-0.2417	-0.1490	0.0434	0.1851	-0.3017
p-value	0.3047	0.5306	0.8557	0.4347	0.1961
b. MS with No/Mild MR					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	0.1108	-0.4482	0.4970	0.1335	-0.2498
p-value	0.5899	0.0217	0.0098	0.5156	0.2184
c. MS with No/Mild/Moderate MR					
	e' (in cm/s)	a' (in cm/s)	e'/a' ratio	E/e' ratio (x10)	Sm (in cm/s)
Regression	0.0242	-0.3302	0.3663	0.1280	-0.1728
p-value	0.8776	0.0306	0.0157	0.4132	0.2739

[Table/Fig-7]: Correlation between TDI values and NT-proBNP levels.
a': Diastasis ventricular filling velocity; e': Early ventricular filling velocity; E: Rapid LV filling velocity; Sm: Peak atrial systolic velocity

Lesion severity	Mild (Mean±SD)	Moderate (Mean±SD)	Severe (Mean±SD)	p-value
At the medial mitral annulus				
a. MR with No/Mild/Moderate MS:				
	Mild MR	Moderate MR	Severe MR	
e' (in cm/s)	7.37±3.03	7.88±2.82	6.01±0.88	0.3211
a' (in cm/s)	8.78±1.15	10.51±3.52	8.17±2.58	0.2582
e'/a'	0.84±0.34	0.87±0.46	0.81±0.31	0.9558
E/e' (x10)	0.24±0.14	0.25±0.14	0.32±0.17	0.5822
Sm (in cm/s)	9.15±2.29	7.93±1.57	7.61±1.25	0.2898
b. MS with No/Mild MR				
	Mild MS	Moderate MS	Severe MS	
e' (in cm/s)	6.41±1.33	7.59±3.37	7.91±2.85	0.7771
a' (in cm/s)	9.88±0.59	8.03±0.56	9.10±4.70	0.8624
e'/a'	0.65±0.17	0.93±0.34	1.03±0.53	0.5852
E/e' (x10)	0.16±0.09	0.29±0.13	0.33±0.22	0.5363
Sm (in cm/s)	11.15±0.90	7.80±1.51	7.73±1.49	**0.0160**
c. MS with No/Mild/Moderate MR				
	Mild MS	Moderate MS	Severe MS	
e' (in cm/s)	6.67±1.04	7.79±3.12	7.63±2.62	0.8107
a' (in cm/s)	9.67±0.56	9.71±3.41	9.56±4.53	0.9946
e'/a'	0.69±0.14	0.91±0.45	0.95±0.51	0.6689
E/e' (x10)	0.16±0.06	0.28±0.14	0.33±0.19	0.2386
Sm (in cm/s)	10.16±1.82	7.71±1.53	7.96±1.67	0.0762
At the lateral mitral annulus				
a. MR with No/Mild/Moderate MS:				
	Mild MR	Moderate MR	Severe MR	
e' (in cm/s)	8.91±3.71	7.88±1.70	9.31±4.25	0.6619
a' (in cm/s)	7.69±3.50	7.66±2.74	10.19±5.03	0.3804
e'/a'	1.31±0.58	1.21±0.73	1.01±0.56	0.7114
E/e' (x10)	0.21±0.16	0.22±0.06	0.22±0.12	0.9864
Sm (in cm/s)	8.37±1.56	8.63±1.81	7.93±2.01	0.7479
b. MS with No/Mild MR				
	Mild MS	Moderate MS	Severe MS	
e' (in cm/s)	7.99±0.59	9.35±4.17	8.15±2.57	0.7226
a' (in cm/s)	11.15±0.29	5.62±1.80	8.55±3.66	0.1569
e'/a'	0.72±0.03	1.63±0.27	1.11±0.55	0.1030
E/e' (x10)	0.12±0.04	0.25±0.16	0.30±0.16	0.2874
Sm (in cm/s)	9.76±1.34	7.89±1.14	8.23±1.57	0.3422
c. MS with No/Mild/Moderate MR				
	Mild MS	Moderate MS	Severe MS	
e' (in cm/s)	8.20±0.56	8.33±2.85	7.97±2.46	0.9141
a' (in cm/s)	11.15±0.21	6.33±2.13	8.79±3.24	**0.0194**
e'/a'	0.74±0.04	1.45±0.65	1.05±0.54	0.0659
E/e' (x10)	0.12±0.02	0.25±0.09	0.30±0.14	0.0550
Sm (in cm/s)	9.95±0.99	8.06±1.53	8.42±1.96	0.2933
At the tricuspid annulus				
a. MR with No/Mild/Moderate MS:				
	Mild MR	Moderate MR	Severe MR	
e' (in cm/s)	12.52±5.24	12.01±3.81	8.97±2.91	0.2374

a' (in cm/s)	11.64±7.52	13.96±5.81	15.09±4.78	0.6160
e'/a'	1.60±1.23	1.04±0.65	0.73±0.62	0.2167
E/e' (x10)	0.14±0.08	0.15±0.07	0.22±0.11	0.2377
Sm (in cm/s)	12.18±5.33	12.09±2.95	9.69±2.07	0.3401
b. MS with No/Mild MR				
	Mild MS	**Moderate MS**	**Severe MS**	
e' (in cm/s)	12.72±8.78	10.92±4.42	11.07±3.55	0.8522
a' (in cm/s)	7.03±6.80	10.87±7.72	13.29±5.94	0.5283
e'/a'	0.70±0.24	1.74±1.40	1.19±1.04	0.5042
E/e' (x10)	0.09±0.03	0.20±0.07	0.21±0.13	0.3683
Sm (in cm/s)	16.75±4.72	9.27±2.71	10.30±1.35	**0.0002**
c. MS with No/Mild/Moderate MR				
	Mild MS	**Moderate MS**	**Severe MS**	
e' (in cm/s)	11.56±6.53	11.77±4.17	11.31±3.22	0.9421
a' (in cm/s)	17.31±4.83	11.94±6.51	12.02±5.87	0.3415
e'/a'	0.64±0.20	1.40±1.00	1.32±0.97	0.4635
E/e' (x10)	0.09±0.02	0.18±0.07	0.21±0.11	0.1634
Sm (in cm/s)	16.49±3.37	10.29±2.57	10.15±1.70	**0.0001**

[Table/Fig-8]: Association between TDI parameters and severity of valvular lesion.

With the severity of MS [Table/Fig-5]: At the lateral mitral annulus, the a' velocity decreased from 11.15±0.21 cm/s to 8.79±3.24 cm/s as the severity of MS increased (p=0.0194). At the tricuspid annulus, only the S'm velocity was observed to significantly decrease (p<0.0001) with increasing severity of MS.

In summary, at the tricuspid annulus in subgroups B and C, as the NYHA class of symptoms worsened and NT-proBNP levels increased, the a' velocity decreased and the e'/a' ratio increased, with no significant association found with the severity of MS as assessed by SET.

DISCUSSION

Contrary to the prevailing belief, there has been no significant decline in the prevalence of RHD in low- and middle-income countries [22]. In absolute numbers, India, often referred to as the RHD capital of the world [23], accounts for one-third of the total global cases of RHD [24], which are likely under-reported [25].

The 2020 ACC/AHA guidelines for the management of patients with VHD [26]. The strategies for primary and secondary prevention of RHD remain undefined. Furthermore, the dynamic interactions between structural and functional changes in the ventricles and the vascular system are not fully understood. Newer measures of Left Ventricular (LV) structure (such as volumes instead of dimensions) and function (like LV Strain) are under-studied in this population. Therefore, this study on RHD patients aims to address these evidence gaps TDI parameters, which exhibit less inter-reader variability and are independent of pre-load and after-load [27].

An additional strength of this study is its non-lesion-specific inclusion criteria. All RHD patients, regardless of the lesion type, were enrolled, and Mitral Valve Diseases (MVD) were classified accordingly. This approach mirrors the more common and practical clinical scenario, as opposed to research that focuses on isolated lesions.

TDI parameters proved useful in evaluating Left Atrial Appendage (LAA) systolic function [28,29], even when global systolic function appeared normal. In rheumatic AS, the E/e' ratio inversely correlated with patient functional capacity and could serve as a marker for early aortic valve replacement surgery [30]. Similar findings were observed for isolated MS, where TDI parameters worsened (both systolic as well as diastolic velocities) despite normal SET assessments [31]. In line with these findings, the present study also demonstrated a significant reduction in the Sm velocities at the tricuspid annulus in Group-C as valve lesion severity (by SET) progressed from mild to moderate.

RV function is crucial to assess in MS, as it influences the symptomatic status of patients. Studies have reported mixed findings concerning systolic TDI velocities when analysed against patients' clinical status. This study aligns with the results of Saricam E et al., where no statistically significant difference was observed between symptomatic and asymptomatic patient groups [32]. However, a decrease in Sm velocity was noted at the tricuspid annulus, from 12.33±2.61 cm/s in NYHA I to 8.58±2.27 cm/s in NYHA IV (p=0.2054), a reduction also reported by Ahmed MK et al., as statistically significant [33].

Regarding diastolic function of the RV, the present study reported that at the tricuspid annulus, the a' velocity decreased and the e'/a' ratio increased from 0.96±0.40 in NYHA I to 2.41±1.00 in NYHA IV (p=0.0210) in subgroup-C. This is in contrast to other studies [13,32,33], which found that the e'/a' ratio was significantly lower in symptomatic patients compared to asymptomatic ones. However, the current study differs markedly from previous research. We graded the functional status of patients from NYHA I to IV, as opposed to dichotomising patients as simply symptomatic or asymptomatic. Additionally, this study included patients with MVD rather than focusing on a single isolated lesion, such as MS. Lastly, this study demonstrated internal validation, which will be elaborated upon later.

To the best of our knowledge, there are no studies directly correlating TDI parameters with NT-proBNP levels in patients with Rheumatic Heart Disease (RHD). Kotby AA et al., investigated the role of NT-proBNP and TDI in patients with Acute Rheumatic Carditis (ARC). They found that NT-proBNP levels were elevated in ARC and decreased with the resolution of the condition in paediatric patients [34]. The current study reveals that as NT-proBNP levels rise, TDI parameters deteriorate, particularly at the tricuspid annulus. Specifically, in Group-C, as the clinical status of the patient deteriorates (indicated objectively by increasing NT-proBNP levels), the a' velocity at the tricuspid annulus decreases (regression coefficient r=-0.3302, p=0.0306), and the e'/a' ratio increases (regression coefficient r=-0.3663, p=0.0157).

Spectral mitral annular E/e' velocities measured using TDI have demonstrated a linear correlation with invasive Left Ventricular (LV) diastolic pressures, regardless of LV ejection fraction, heart rate, and rhythm [34]. As diastolic dysfunction progresses, there is a marked reduction in the a' velocities at the mitral annuli [35]. Given that diastolic filling patterns in the Right Ventricle (RV) are similar to those in the LV, analogous trends are expected at the tricuspid annulus [35]. In mild diastolic dysfunction, there is a reversal of the e'/a' ratio, with the atrial contribution becoming more significant in ventricular filling. With moderate diastolic dysfunction, a pseudo-normalisation pattern emerges, where diastolic filling velocities return to near-normal values [35]. In severe diastolic dysfunction, both e' and a' velocities are significantly reduced. Consistent with this pattern of diastolic worsening, the present study confirms the trend of decreasing RV a' velocity.

The study has undergone internal validation, as justified by the following: The study demonstrates a statistically significant increase in serum NT-proBNP levels corresponding to the worsening NYHA class of dyspnoea. Therefore, the trends of TDI parameters observed independently with NYHA Class and serum NT-proBNP levels are concordant. That is, as the NYHA class of symptoms in a patient worsens, the a' velocities decrease, and the e'/a' ratio increases. Consequently, a similar trend should be expected when these TDI parameters are correlated with increasing levels of serum NT-proBNP. This observation was found to be statistically significant.

Limitation(s)

The study did not differentiate between patients who were newly diagnosed with RHD and those who had been under previous medical management for the condition. With a relatively small

sample size, the study cannot confidently generalise its findings to the broader population of RHD patients across the country.

CONCLUSION(S)

According to the current study's findings, it was observed that in patients with RHD, especially with MS and co-existent MR, the TDI findings, notably the e'/a' ratio and the a' velocity at the tricuspid annulus, showed a statistically significant increase correlating with the worsening of symptom class. Furthermore, these parameters did not correlate with the severity of the valvular lesion as measured by the SET. Hence, TDI parameters like the tricuspid annular e'/a' ratio, along with serum NT-proBNP levels, should be regularly assessed instead of the commonly used E/e' ratio, to detect earlier right heart involvement. Deciding whether such patients should be selected for earlier surgical intervention would necessitate a larger-scale study in the future with different study designs.

REFERENCES

[1] O'Gara PT, Loscalzo J. Aortic Stenosis. In: Loscalzo J, Fauci A, eds. Harrison's Principles of Internal Medicine (21st edition). New York: McGraw-Hill Education, 2022.
[2] Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. Lancet. 2005;366(9480):155-68.
[3] Leal MT, Passos LS, Guarçoni FV, Aguiar JM, Silva RB, Paula TM, et al. Rheumatic heart disease in the modern era: Recent developments and current challenges. Rev Soc Bras Med Trop. 2019:52:e20180041.
[4] Lawrence JG, Carapetis JR, Griffiths K, Edwards K, Condon JR. Acute rheumatic fever and rheumatic heart disease: Incidence and progression in the Northern Territory of Australia, 1997 to 2010. Circulation. 2013;128(5):492-501.
[5] Remenyi B, ElGuindy A, Smith SC Jr, Yacoub M, Holmes DR Jr. Valvular aspects of rheumatic heart disease. Lancet. 2016;387(10025):1335-46.
[6] New York Heart Association, Harvey RM. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Little, Brown; 1994. https://search.worldcat.org/title/Nomenclature-and-criteria-for-diagnosis-of-diseases-of-the-heart-and-great-vessels/oclc/29430883.
[7] Sharma J, Goel PK, Pandey CM, Awasthi A, Kapoor A, Tewari S, et al. Intermediate outcomes of rheumatic mitral stenosis post-balloon mitral valvotomy. Asian Cardiovasc Thorac Ann. 2015;23(8):923-30.
[8] Lindman BR, Clavel MA, Mathieu P, Iung B, Lancellotti P, Otto CM, et al. Calcific aortic stenosis. Nature Reviews Disease Primers. 2016;2(1):01-28.
[9] Lindman BR, Arnold SV, Madrazo JA, Zajarias A, Johnson SN, Pérez JE, et al. The adverse impact of diabetes mellitus on left ventricular remodeling and function in patients with severe aortic stenosis. Circulation: Heart Failure. 2011;4(3):286-92.
[10] Briand M, Dumesnil JG, Kadem L, Tongue AG, Rieu R, Garcia D, et al. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: Implications for diagnosis and treatment. J Am Coll Cardiol. 2005;46(2):291-98.
[11] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur J Echocardiogr. 2016;17(12):1321-60.
[12] Plana JC, Desai MY, Klein AL. Assessment of diastolic function by echocardiography (chap. 11). The practice of clinical echocardiography (4e éd.). Philadelphie: Elsevier/Saunders. 2012.
[13] Mukherjee SS, Jose J, George P, Samuel V. Right ventricular diastolic function assessment by Tissue Doppler in mitral stenosis-Correlation with functional capacity. J Indian Coll Cardiol. 2015;5(2):107-11.
[14] Iltumur K, Karabulut A, Yokus B, Yavuzkir M, Taskesen T, Toprak N. N-terminal proBNP plasma levels correlate with severity of mitral stenosis. J. Heart Valve Dis. 2005;14(6):735-41.
[15] Polat TB, Yalcin Y, Erdem A, Zeybek C, Akdeniz C, Celebi A. Tissue Doppler imaging in rheumatic carditis. Cardiol Young. 2014;24(2):359-65.
[16] Guven S, Sen T, Tufekcioglu O, Gucuk E, Uygur B, Kahraman E. Evaluation of left ventricular systolic function with pulsed wave tissue Doppler in rheumatic mitral stenosis. J Cardiol. 2014;21(1):33-38.
[17] Shelton RJ, Clark AL, Goode K, Rigby AS, Cleland JG. The diagnostic utility of N-terminal pro-B-type natriuretic peptide for the detection of major structural heart disease in patients with atrial fibrillation. Eur. Heart J. 2006;27(19):2353-61.
[18] Oremus M, Don-Wauchope A, McKelvie R, Santaguida PL, Hill S, Balion C, et al. BNP and NT-proBNP as prognostic markers in persons with chronic stable heart failure. Heart Failure Reviews. 2014;19(4):471-505.
[19] Saxena A, Desai A, Narvencar K, Ramakrishnan S, Thangjam RS, Kulkarni S, et al. Echocardiographic prevalence of rheumatic heart disease in Indian school children using World Heart Federation criteria-A multisite extension of RHEUMATIC study (the e-RHEUMATIC study). Int J Cardiol. 2017;249:438-42.
[20] Remenyi B, Carapetis J, Stirling JW, Ferreira B, Kumar K, Lawrenson J, et al. Inter-rater and intra-rater reliability and agreement of echocardiographic diagnosis of rheumatic heart disease using the World Heart Federation evidence-based criteria. Heart Asia. 2019;11(2):e011233.
[21] Unger P, Clavel MA, Lindman BR, Mathieu P, Pibarot P. Pathophysiology and management of multivalvular disease. Nature Reviews Cardiology. 2016;13(7):429-40.
[22] Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, regional, and national burden of rheumatic heart disease, 1990 2015. N Engl J Med. 2017;377(8):713-22.
[23] Karthikeyan G. Rheumatic heart disease in India: Declining, but not fast enough. Natl Med J India. 2017;30(5):247-48.
[24] Gupta R, Panwar RB, Sharma A, Panwar SR, Rao RS, Gupta BK. Continuing Burden of Rheumatic Heart Disease in India. J Assoc Physicians India. 2020;68(10):60-65.
[25] Negi PC, Sondhi S, Asotra S, Mahajan K, Mehta A. Current status of rheumatic heart disease in India. Indian Heart J. 2019;71(1):85-90.
[26] Otto C, Nishimura R, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2021;77(4):e25-e197.
[27] Bess RL, Khan S, Rosman HS, Cohen GI, Allebban Z, Gardin JM. Technical aspects of diastology: Why mitral inflow and tissue doppler imaging are the preferred parameters? Echocardiography: A Journal of Cardiovascular Ultrasound and Allied Techniques. 2006;23(4):332-39.
[28] Rajasekhar D. Echocardiographic assessment of left atrial appendage function in patients with Mitral Stenosis by Tissue Doppler Velocity Imaging (Doctoral dissertation, Madras Medical College, Chennai) 2009. [http://repository-tnmgrmu.ac.in/873/1/160200109rajasekhar.pdf].
[29] Gurlertop Y, Yilmaz M, Acikel M, Bozkurt E, Erol MK, Senocak H, et al. Tissue Doppler properties of the left atrial appendage in patients with mitral valve disease. Echocardiography. 2004;21(4):319-24.
[30] Krishnakumar C. Utility value of tissue doppler in Aortic stenosis; E/EA values predict symptoms and functional capacity in patients with Aortic stenosis (Doctoral dissertation, Madras Medical College, Chennai) 2010. [http://repository-tnmgrmu.ac.in/874/1/160200110krishnakumar.pdf].
[31] Özer N, Can I, Atalar E, Sade E, Aksöyek S, Övünç K, et al. Left ventricular long-axis function is reduced in patients with rheumatic mitral stenosis. Echocardiography. 2004;21(2):107-12.
[32] Saricam E, Ozbakir C, Yildirim N, Tufekcioglu O, Ocal A, Bascil S, et al. Evaluation of the relationship between functional capacity and right ventricular diastolic function in patients with isolated mitral stenosis and sinus rhythm: A tissue Doppler study. Echocardiography. 2007;24(2):134-39.
[33] Ahmed MK, Reda AA, Ibrahim MH. Right ventricular function and symptomatology in patients with isolated mitral stenosis: A doppler tissue imaging study. The Egyptian Heart Journal. 2015;67(1):41-46.
[34] Kotby AA, El-Shahed GS, Elmasry OA, El-Hadidi IS, El Shafey RN. N-terminal proBNP levels and tissue doppler echocardiography in acute rheumatic carditis. ISRN Pediatr. 2013;2013:970394.
[35] Otto CM. Ventricular Diastolic filling and function. In: Textbook of Clinical Echocardiography (6th Edition). Haryana: Elsevier, 2020.

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