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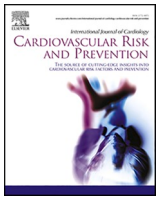

Differentiation of the severity of rheumatic mitral stenosis using dimensionless index and its association with outcomes

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ABSTRACT

Introduction: The severity of mitral stenosis (MS) is commonly assessed using mitral valve area (MVA) measured with transthoracic echocardiography (TTE). The dimensionless index (DI) of mitral valve (MV) was recently studied in degenerative MS. We evaluated DI MV in rheumatic MS and studied its relationship with clinical outcomes.

Methods: We studied 406 cases of rheumatic MS in a retrospective single centre cohort study, with 174 in a derivation cohort, 121 in a TTE validation cohort, and 111 in a transoesophageal echocardiography (TEE) validation cohort. DI MV was calculated by dividing the left ventricular outflow tract pulsed-wave Doppler time-velocity integral (TVI) by the MV continuous-wave Doppler TVI. DI MV was compared against MV area using the two-dimensional planimetry, pressure half-time and continuity equation methods, or, in the TEE validation cohort, TEE-derived three-dimensional planimetry. Severe MS was defined as an MV area $\leq$1.5 cm^2. Outcomes pertaining to all-cause death and mitral valve intervention were studied in the former two cohorts.

Results: All-in-all, 231 patients (56.9 %) across the three cohorts had severe MS. In the derivation cohort, ROC analysis showed that DI MV could accurately classify MS severity (AUC = 0.838, 95 % CI, 0.780–0.897, $p <$ 0.001). DI MV $\leq$ 0.25 and DI MV $\geq$ 0.40 had high specificity for identifying severe (93.7 %) and non-severe MS (93.7 %) respectively. In the validation cohorts, these respectively showed similar specificity for identifying severe (93.8 %) and non-severe MS (91.4 %). In the derivation and TTE validation cohorts, the median follow up duration was 6.32 years (interquartile range, 4.22–10.3 years) with 90 deaths (30.5 %) and 50 patients (17.0 %) undergoing MV intervention. DI MV was univariately significant (HR = 0.075, 95 % CI 0.0215–0.378, $p = 0.002$) in Cox regression for a composite outcome of death and MV intervention. DI MV remained independently associated with the composite outcome in multivariate analysis.

Conclusion: DI MV can help rule-in or rule-out severe MS with high specificity, and is independently associated with composite outcomes of death and MV intervention.

1. Introduction

Mitral stenosis (MS) is a frequently encountered valvular problem which predominantly arises as a sequelae of rheumatic heart disease, especially in the developing world where rheumatic fever remains prevalent [1,2]. Recently, degenerative mitral stenosis, arising from extensive calcification of the mitral annulus with encroachment on the mitral leaflets, was recognised as an important cause of mitral stenosis [3,4].

Transthoracic echocardiography (TTE) remains the main tool for the assessment of MS. Measurement of mitral valve area (MVA) from multiple methods provides key information on the severity of MS but these different methods of MVA assessment face their own limitations [5–9]. While two-dimensional planimetry is considered the reference

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measurement for assessing MVA, its accuracy relies on the ability to visualise the narrowest cross-sectional area of the MV orifice which can be time-consuming and pose difficulty even for experienced sonographers owing to technical difficulty and anatomical factors [6,10]. The PHT method is affected by abnormal atrioventricular compliance, such as in patients with left ventricular diastolic dysfunction. Associated aortic regurgitation (AR) can also lead to rapid increases in left ventricular pressures and confound PHT calculations [7,11]. The continuity equation (CE) method relies on multiple measurements which is a potential source of error [12,13]. It is also inaccurate in patients with significant mitral regurgitation (MR) or AR [7,9]. Lastly, the proximal isovelocity surface area (PISA) method is technically demanding due to the need for an angle correction factor α which needs to be manually measured, hence limiting its practicality [7,14].

The limitations of these various methods to calculate MVA can yield discrepant results, and clinicians typically rely on a combination of different methods to assess MVA [5,6]. Transoesophageal echocardiography (TEE) allows very precise measurement of MVA via three-dimensional TEE (3D TEE) and it has been extensively validated against MVA measurements using two-dimensional planimetry and pressure half-time [15–17]. Today, 3D TEE is increasingly considered as the gold standard measurement of MVA [9,18,19]. Unfortunately, TEE is semi-invasive which limits its routine widespread use. Therefore, when discrepant results from the various methods used to measure MVA are encountered, it can be challenging and time-consuming for the echocardiographer to adjudicate the final severity of the valve lesion from the available TTE data.

Recently, the dimensionless index (DI) of the MV, calculated by dividing the LVOT time-velocity integral (TVI) by the MV TVI, was described as an accurate measure of the severity of degenerative MS [20]. The similar dimensionless velocity index (DVI) is frequently used to assess for valve stenosis in native aortic valves as well as prosthetic mitral and aortic valves [21–24]. Despite common usage of the DVI in the evaluation of other forms of stenotic valvular disease, to our knowledge, the analogous DI MV has not been previously evaluated in the context of rheumatic MS. We hypothesized that DI MV may be useful in identifying the severity of rheumatic mitral stenosis.

2. Methods

We studied 406 cases of rheumatic MS in a retrospective single center cohort study. The patients were divided into three cohorts:

1 A cohort of 176 cases of isolated rheumatic MS who underwent TTE, termed the derivation cohort'.
2 A second cohort of 121 cases of rheumatic MS who underwent TTE termed the 'TTE validation cohort'.
3 A third cohort of 111 cases of rheumatic MS who underwent both TTE and TEE examinations, termed the 'TEE validation cohort'.

The study protocol was approved by our center's Institutional Review Board and conforms to the ethical principles laid out in the 1975 Declaration of Helsinki. The Institutional Review Board waived the requirement for informed consent to be obtained as this was a retrospective study with no potentially identifiable data.

2.1. Echocardiographic methods

For all cases, echocardiographic data were obtained from the electronic medical records and echocardiography databases. We calculated the DI MV by dividing the LVOT TVI by the MV VTI. In all cohorts, we measured MVA using two-dimensional planimetry and PHT methods. Two-dimensional planimetry was determined by the direct measurement of the area of the mitral valve orifice in diastole in the short-axis view. The MVA by PHT method was determined according to the formula *MVA by pressure half-time (cm^2) = 220 ÷ PHT (ms)* where the PHT measurement was obtained using the E wave downslope from the mitral inflow Doppler pulse-wave signal. MVA using the CE method was obtained in the derivation and TEE validation cohorts, but not the TTE validation cohort, as it included patients with significant MR or AR. This was calculated according to the formula *MVA by continuity equation (cm^2) = LVOT VTI (cm) × LVOT diameter (cm) ÷ MV VTI (cm)*. For Doppler-related measurements, measurements from three cardiac cycles were averaged when the patient was in sinus rhythm, while five cardiac cycles were used when the patient was in atrial fibrillation [6]. Lastly, in the TEE validation cohort, three-dimensional MVA was obtained by multiplanar reconstruction or direct planimetry of the MV orifice according to our institution's protocol for TEE studies [15]. Measurements were independently verified by an experienced echocardiographer (YTC) who was blinded to clinical data and other echocardiographic parameters. For the purposes of reliability analyses, we randomly selected a subset of 10 patients to have the DI MV measurements repeated by a second investigator on two separate occasions.

Severe MS was defined as an MVA ≤1.5 cm [25]. In the derivation cohort, we considered patients to have severe MS if the MVA was ≤1.5 cm^2 by all three methods ie. planimetry, PHT and CE. In the TTE validation cohorts, patients were determined to have severe MS if MVA was ≤1.5 cm^2 by both planimetry and PHT methods, while in the TEE validation cohort, three-dimensional MVA was used as the gold standard.

2.2. Clinical and outcome data

Clinical and outcomes data were obtained from the electronic medical records. Outcomes were studied in the derivation and the TTE validation cohorts but not in the TEE validation cohort, as the latter group included many cases who underwent TEE as part of pre-procedure assessment for MV intervention. The composite of all-cause mortality and mitral valve intervention was the primary endpoint studied. We also evaluated the components of the composite outcome (all-cause mortality and mitral valve intervention) as individual outcomes of interest.

2.3. Statistical analyses

Bivariate correlation analysis and calculation of Pearson's correlation coefficient was performed to evaluate the correlation between the various methods of determining severity of MS in the study cohorts. Receiver operating characteristic (ROC) analysis was performed in the derivation cohort to determine the sensitivity and specificity of DI MV in identifying severe MS. We also identified cut off values to rule-in and rule-out severe MS. We then validated these cut-off values in the TTE and the TEE validation cohorts. Intra- and inter-observer variability of DI MV was assessed by reliability analysis involving intra-class correlation coefficients (ICC) with 95 % confidence intervals [25].

We analysed clinical outcomes by performing Cox regression analysis using clinical and echocardiographic parameters in a univariate fashion against the composite outcomes of death and MV intervention, which identified a set of variables which were significantly associated with the composite outcome. These variables, along with biologically important variables (age and sex) were then used to construct a multivariate Cox regression model to study associations with the composite outcome. We noted that the variables which were univariately significant included DI MV and other variables which were directly related to the severity of MS, namely MVA by planimetry, MVA by PHT and the transmitral pressure gradient. We identified statistically significant correlations between DI MV and these other variables to which the DI MV was closely related, and therefore did not select these other variables for inclusion in the final multivariate model.

Continuous variables are presented as mean ± standard deviation and categorical variables as frequency and percentages. *p*-values less than 0.05 were deemed statistically significant. Statistical analysis was performed with IBM SPSS Statistics Version 23 (IBM Corp., Armonk, NY, USA).

3. Results

The baseline clinical characteristics for the study cohorts are presented in Table 1. The study population in aggregate is predominantly female with 71.9 % of the overall cohort being of female sex, with a mean age of 57.5 (±13.5) years. In total, 153 (37.7 %) of patients in the study cohort were symptomatic at the time of study inclusion; 35 (20.1 %) in the derivation cohort, 22 (18.2 %) in the TTE validation cohort, and 96 (86.5 %) in the TEE validation cohort. The median follow up time for the derivation and TTE validation cohorts was 6.32 years (interquartile range, 4.22–10.3 years).

Table 2 shows the echocardiographic data for the three cohorts. In total, 231 patients (56.9 %) across the three cohorts had severe MS. In the derivation cohort, 79 patients (45.4 %) had severe MS, while in the TTE validation cohort 50 (21.6 %) of patients had severe MS. The TEE cohort had relatively more patients with severe MS (102 patients, 91.9 %). Across the three cohorts, 286 (70.4 %) patients had isolated rheumatic MS, while 120 (29.6 %) had mixed valvular disease, which we defined as the presence of MR, aortic stenosis (AS), or AR of greater-than-mild severity. Amongst those with mixed valvular disease, in addition to rheumatic MS, 77 (18.9 %) had MR only, 32 (7.9 %) had AS only, and 4 (1.7 %) had AR only. Six (1.5 %) patients had both MR as AS, and 1 patient had both AS and AR. In the TEE validation cohort, the median time between the referenced TTE study and the TEE study was 28 (IQR 7 to 162) days.

3.1. Derivation cohort

In the derivation cohort, we found significant correlation between existing methods of MVA assessment (MVA (planimetry) and MVA (PHT), $r = 0.641$, $p < 0.001$; MVA (planimetry) and MVA (CE) $r = 0.679$, $p < 0.001$, and MVA (PHT) and MVA (CE), $r = 0.579$, $p < 0.001$). When DI MV was compared against these measurements of MVA, the correlation coefficient between DI MV and MVA (planimetry) was $r = 0.619$, $p < 0.001$; between DI MV and MVA (PHT) $r = 0.579$, $p < 0.001$; and between DI MV and MVA (CE), $r = 0.897$; $p < 0.001$. ROC analysis for the performance of DI MV to correctly identify severe MS in the derivation cohort is shown in Fig. 1. The area-under-the-curve (AUC) value for the ROC curve was 0.838 (95 % CI 0.780–0.897, $p < 0.001$). No threshold value was able to identify severe MS (MVA $\leq$1.5 cm^2) with both sensitivity and specificity greater than 80 %. MV DI $\leq$ 0.34 had the best combination of sensitivity and specificity (78.5 % and 75.8 % respectively). However, MV DI $\leq$ 0.25 and MV DI $\geq$ 0.40 had high specificity for identifying severe MS ("rule in" severe MS) and non severe MS ("rule out" severe MS), as shown in Table 3.

3.2. Validation cohorts

Correlation analysis in the TTE validation cohort showed that, for DI MV and MVA (planimetry), $r = 0.441$, $p < 0.001$; while for DI MV and MVA (PHT), $r = 0.394$, $p < 0.001$. In the TEE validation cohort, the correlation between the DI MV and the MVA by 3D planimetry was $r = 0.648$; $p < 0.001$. The performance of these cut-off values for identifying severe and non-severe MS was then evaluated in our validation cohorts as shown in Table 3. DI MV $\leq$ 0.25 for severe MS showed 93.8 % specificity when the two validation cohorts were pooled. DI MV $\geq$ 0.40 for non-severe MS showed 91.4 % specificity in the pooled validation cohorts.

3.3. Subgroup analysis for patients with mixed valve disease

We subsequently compared the performance of the DI MV with patients with or without significant MR and AS across the three study cohorts in a pooled fashion. The performance of the DI MV in the subgroup of patients with AR was not evaluated due to small numbers of patients with significant concomitant AR in the study cohorts.

For patients with significant MR, the AUC was 0.792 (95 % CI 0.689–0.874), while for those without significant MR, the AUC was 0.845 (95 % CI 0.801–0.883), $p = 0.343$. For those with significant AS, the AUC was 0.829 (95 % CI 0.674–0.930), while for patients without

Table 1
Baseline clinical characteristics for the study cohorts.

	Overall (n = 406)	Derivation Cohort (n = 174)	TTE Validation Cohort (n = 121)	TEE Validation Cohort (n = 111)	*p*-value
Clinical variable					
Age (years)	57.5 (±13.5)	53.5 (±12.6)	58.6 (±14.0)	62.5 (±12.7)	**<0.001**
Female sex	292 (71.9 %)	117 (67.2 %)	93 (76.9 %)	82 (73.9 %)	0.169
Height (cm)	157 (±8.4)	158.5 (±8.8)	157.2 (±7.8)	157.5 (±7.7)	0.341
Weight (kg)	61.1 (±14.2)	61.0(±13.6)	60.3 (±13.1)	62.3 (±16.3)	0.548
BSA (m^2)	1.63 (±0.21)	1.63 (±0.20)	1.61 (±0.19)	1.64 (±0.23)	0.648
Blood pressure (mmHg)	127.7 (±22.0)/70.7 (±11.4)	126.6 (±20.3)/71.9 (±11.4)	128.3 (±24.7)/69.2 (±11.6)	128.6 (±21.5)/70.4 (±11.2)	0.706/ 0.133
Heart rate (beats per minute)	78.0 (±18.9)	74.9 (±16.9)	81.3 (±17.9)	79.2 (±22.0)	**0.013**
Symptomaticity at time of inclusion	153 (37.7 %)	35 (20.1 %)	22 (18.2 %)	96 (86.5 %)	**<0.001**
Hypertension	167 (41.1 %)	69 (39.7 %)	54 (44.6 %)	44 (39.6 %)	0.647
Hyperlipidemia	147 (36.2 %)	57 (32.8 %)	53 (43.8 %)	37 (33.3 %)	0.116
Diabetes mellitus	95 (23.4 %)	40 (23.0 %)	37 (30.6 %)	18 (16.2 %)	**0.035**
Ischemic heart disease	59 (14.5 %)	27 (15.5 %)	15 (12.4 %)	17 (15.3 %)	0.728
Stroke or transient ischemic attack	54 (13.3 %)	19 (10.9 %)	20 (16.5 %)	15 (13.5 %)	0.377
Atrial fibrillation	225 (55.4 %)	95 (54.6 %)	70 (57.9 %)	60 (54.1 %)	0.810
Heart failure	81 (20.0 %)	29 (16.7 %)	27 (22.3 %)	25 (22.5 %)	0.357
Chronic kidney disease	35 (8.6 %)	13 (7.5 %)	16 (13.2 %)	6 (5.4 %)	0.082
Antiplatelet	118 (29.1 %)	52 (29.9 %)	33 (27.3 %)	33 (29.7 %)	0.874
Anticoagulation	195 (48.0 %)	79 (45.4 %)	60 (49.6 %)	56 (50.5 %)	0.651
Beta-blocker	212 (52.2 %)	85 (48.9 %)	66 (54.5 %)	61 (55.0 %)	0.500
Calcium-channel-blocker	45 (11.1 %)	18 (10.3 %)	16 (13.2 %)	11 (9.9 %)	0.666
Diuretic	113 (27.8 %)	46 (26.4 %)	39 (32.2 %)	28 (25.2 %)	0.425
ACE-I/ARB	94 (23.2 %)	49 (28.2 %)	30 (24.8 %)	15 (13.5 %)	**0.015**
MRA	12 (3.0 %)	3 (1.7 %)	3 (2.5 %)	6 (5.4 %)	0.188

Data are presented in the form of number (percentage), or mean value (±1 standard deviation).
Abbreviations: ACE-I; angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; MRA, mineralocorticoid receptor antagonist.

Table 2
Baseline echocardiographic parameters for the study cohorts.

	Overall (n = 406)	Derivation Cohort (n = 174)	TTE Validation Cohort (n = 121)	TEE Validation Cohort (n = 77)	*p*-value
Echocardiographic Parameters	Mean value (±1 standard deviation)				
Left atrial diameter (mm)	51.4 (±8.4)	49.6 (±8.8)	52.7 (±7.8)	52.0 (±7.94)	0.004
Left atrial volume (ml)	106.0 (±48.7)	96.3 (±46.4)	115.2 (±52.2)	110.6 (±45.5)	0.003
Left atrial volume index (ml/m^2)	66.3 (±32.7)	59.7 (±29.5)	72.4 (±35.5)	69.5 (±32.6)	0.003
Left ventricle mass index (g/m^2)	91.0 (±31.6)	87.6 (±30.0)	98.1 (±30.7)	90.0 (±34.1)	0.035
Left ventricle end diastolic volume (ml)	99.5 (±35.3)	97.4 (±33.1)	106.2 (±38.5)	93.2 (±36.3)	0.021
Left ventricle end systolic volume (ml)	39.4 (±22.0)	39.7 (±21.8)	41.7 (±23.0)	35.5 (±21.4)	0.098
Left ventricle stroke volume (ml)	60.1 (±21.2)	58.4 (±18.3)	64.5 (±24.9)	57.7 (±20.2)	0.022
Left ventricle ejection fraction (%)	57.6 (±9.8)	57.3 (±10.6)	58.0 (±10.4)	57.7 (±7.6)	0.808
Left ventricle outflow tract diameter (mm)	19.8 (±1.9)	19.9 (±1.9)	19.6 (±1.8)	19.8 (±2.1)	0.302
Left ventricle outflow tract pulsed-wave TVI (cm)	18.4 (±6.2)	18.7 (±6.7)	17.7 (±3.8)	19.0 (±7.4)	0.090
Heart rate during echocardiographic study (bpm)	75.7 (±17.8)	74.1(±16.9)	80.5 (±18.9)	72.8 (±16.8)	0.006
Estimated cardiac output (L/min)	4.23 (±1.39)	4.19 (±1.20)	4.38 (±1.43)	4.13 (±1.62)	0.479
Estimated cardiac index (L/min/m^2)	2.61 (±0.84)	2.56 (±0.75)	2.73 (±0.93)	2.54 (±0.90)	0.264
Mitral valve continuous-wave TVI (cm)	57.5 (±18.5)	57.4 (±20.0)	54.2 (±16.3)	61.6 (±17.5)	0.013
Pulmonary artery systolic pressure (mmHg)	46.3 (±16.7)	44.0 (±16.5)	49.5 (±16.6)	47.8 (±15.9)	0.007
MVA by two-dimensional planimetry (cm^2)	1.53 (±0.73)	1.37 (±0.40)	1.57 (±0.57)	1.18 (±0.38)	0.001
MVA by pressure half-time (cm^2)	1.43 (±0.48)	1.51 (±0.54)	1.61 (±0.58)	1.31 (±0.44)	0.390
MVA by continuity equation (cm^2)	1.07 (±0.48)	1.12 (±0.49)	N.A.	0.92 (±0.33)	0.016
MVA by three-dimensional planimetry (cm^2)	N.A.	N.A	N.A	1.11 (±0.40)	N.A
Transmitral mean pressure gradient (mmHg)	16.5 (±6.8)	6.9 (±3.7)	7.8 (±4.1)	8.0 (±3.8)	<0.001
Transmitral maximum pressure gradient (mmHg)	7.4 (±3.9)	14.7 (±6.4)	17.7 (±6.6)	18.1 (±7.0)	0.037
Mitral valve DI	0.333 (±0.115)	0.351 (±0.126)	0.346 (±0.113)	0.328 (±0.133)	<0.001
Moderate or greater mitral regurgitation (%)	N.A.	0 (0.0 %)	70 (57.9 %)	13 (11.7 %)	<0.001
Moderate or greater aortic stenosis (%)	N.A.	1 (0.6 %)	28 (23.1 %)	10 (9.0 %)	<0.001
Moderate or greater aortic regurgitation (%)	N.A.	0 (0.0 %)	0 (0.0 %)	5 (4.5 %)	0.001

Data are presented in the form of mean value (±1 standard deviation).
Abbreviations: DI, dimensionless index; MVA, mitral valve area; TVI, time-velocity integral.

significant AS, the AUC was 0.830 (95 % CI 0.787–0.867), $p = 0.989$.

3.4. Reliability analyses

Using a two-way mixed effects model to determine ICC values, the inter-observer reliability for measurement of DI MV had an ICC value of 0.934 (95 % CI 0.759–0.983) whereas the intra-observer reliability had an ICC value of 0.939 (95 % CI 0.776–0.985).

3.5. Outcome analysis

The composite outcome occurred in 129 (43.7 %) patients, with 90 (30.5 %) deaths during the course of follow up, and 51 (17.3 %) undergoing MV intervention. Of the 51 patients who underwent MV intervention, percutaneous transmitral commissurotomy was performed in 22 patients (43.1 %), while 19 patients underwent mechanical MV replacement (37.3 %), 8 patients (15.7 %) had a bioprosthetic MV replacement and 2 patients (3.9 %) underwent open mitral valvotomy.

The following clinical and echocardiographic variables were statistically significant on univariate analysis: age in years (HR 1.017, 95 % CI 1.003–1.030), history of heart failure (HF) (HR 1.603, 95 % CI 1.068–2.407), DI MV (per 0.01 unit increment in DI MV: HR 0.975, 95 % CI 0.959–0.990), MVA by planimetry in cm^2 (HR 0.451, 95 % CI 0.298–0.682), MVA by PHT in cm^2 (HR 0.589, 95 % CI 0.405–0.857), transmitral gradient in mmHg (HR 1.051, 95 % CI 1.010–1.094), LVEF (HR = 0.976, 95 % CI 0.960–0.992) and lastly PASP (HR = 1.015, 95 % CI 1.005–1.024). All other tested variables, including clinical variables such as diabetes mellitus or atrial fibrillation and echocardiographic variables such as left atrial volume index were not statistically significant.

These associations were mainly driven by MV intervention with the exceptions being that of age, which was associated both with all-cause mortality as well as MV intervention individually, and pulmonary artery systolic pressure (PASP) which was associated with all-cause mortality but not MV intervention. A history of HF was not significantly associated with either all-cause mortality or MV intervention when the clinical endpoints were examined individually.

The results of multivariate analysis incorporating age, sex, history of HF, LVEF, PASP and DI MV demonstrated that age (HR 1.024, 95 % CI 1.009–1.039), PASP (HR = 1.013, 95 % CI 1.003–1.024) and the DI MV (per 0.01 unit increment in DI MV: HR 0.981, 95 % CI 0.964–0.998) were independently associated with the composite outcome. In this model, sex, a prior history of HF and LVEF were not statistically significant.

4. Discussion

Our study demonstrated that: (1) DI MV was significantly associated with severity of MS, (2) DI MV was able to differentiate severe from non-severe MS with a high specificity albeit with only modest sensitivity, (3) DI MV was associated with a composite outcome of death and MV intervention, which is mainly driven by its association with MV intervention. The DI MV is analogous to the DVI which is commonly used for the assessment of stenotic valvular heart disease including native aortic valves as well as prosthetic valves, and is a simplification of the continuity equation which is derived from the principle of conservation of mass. The principle of conservation of mass allows flow across a proximal and a distal region in the heart in the absence of shunts or regurgitant lesions to be equated, hence yielding the continuity equation $A_1 \times V_1 = A_2 \times V_2$ where A_1 and A_2 are the proximal and distal cross sectional areas while V_1 and V_2 are velocities at the proximal and distal regions. Conventionally, one region is taken to be the LVOT and the second region is the valve under investigation. LVOT cross sectional area is estimated by measuring the LVOT diameter and calculating an estimated circular cross sectional area while velocities are obtained by measuring the VTI using Doppler echocardiography at the two regions [22]. A well-known key source of error in the continuity equation is the assumption of a circular geometry of the LVOT in order to use the LVOT

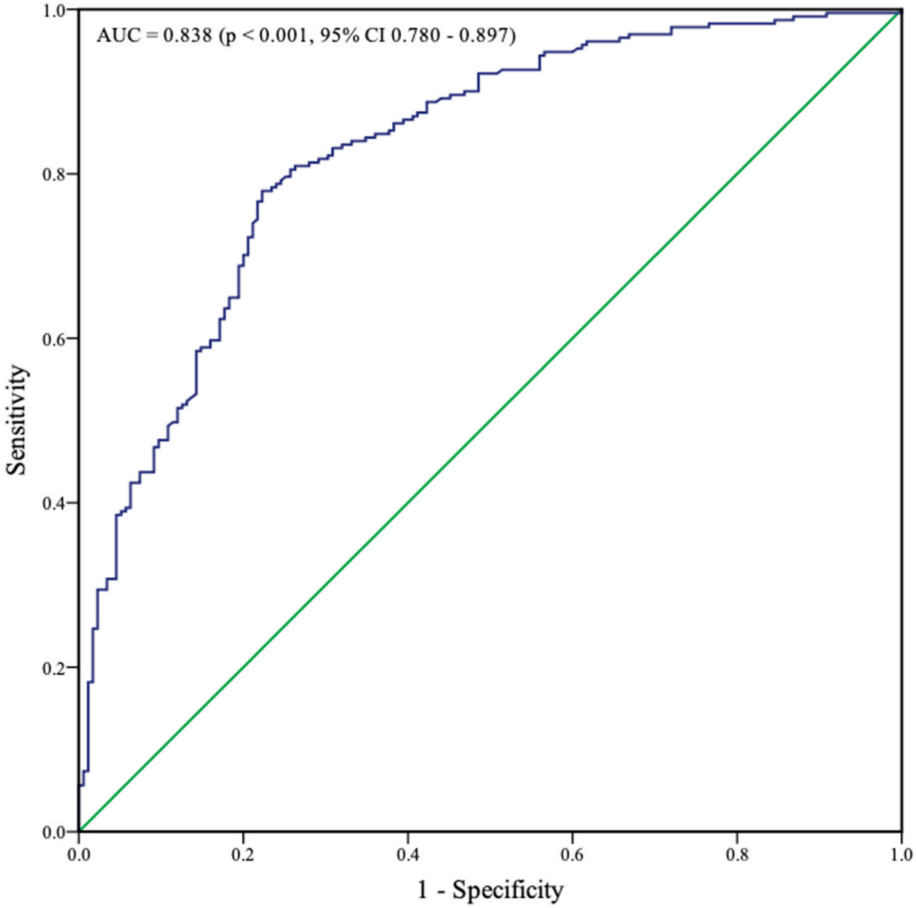

Fig. 1. Receiver operating characteristics curve for Dimensionless Index of Mitral Valve for classification of rheumatic mitral stenosis.
Abbreviations: AUC, area under the curve; CI, confidence interval.

Table 3
Sensitivity and specificity for Dimensionless Index of Mitral Valve for identification of severe (mitral valve area ≤1.5 cm^2) and non-severe (mitral valve area >1.5 cm^2) rheumatic mitral stenosis.

Cohort	DI MV threshold value	Sensitivity (%)	Specificity (%)
Derivation Cohort (n = 174)	≤0.34 (severe MS)	78.5	75.8
	≤0.25 (severe MS)	46.8	93.7
	≥0.40 (non-severe MS)	52.6	93.7
TTE Validation Cohort (n = 121)	≤0.25 (severe MS)	41.3	93.0
	≥0.40 (non-severe MS)	45.1	90.0
TEE Validation Cohort (n = 111)	≤0.25 (severe MS)	38.2	100.0
	≥0.40 (non-severe MS)	44.4	92.2
Combined Validation Cohort (n = 232)	≤0.25 (severe MS)	40.1	93.8
	≥0.40 (non-severe MS)	45.0	91.4

Abbreviations: MS, mitral stenosis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

diameter to estimate its area [22]. The LVOT has been demonstrated to be elliptical in nature which results in the introduction of an error proportional to the square of the inaccuracy in the LVOT measurements [26,27]. The DVI and DI methods, DI = $V_1 \div V_2$, express the velocity at the valve lesion as a ratio to the velocity at the LVOT, and effectively describes the area of the valve under evaluation as a fraction of the area of the LVOT. Commonly, TVI is used in the ratio instead of velocity. Without the need to calculate a reference area in the continuity equation, this method eliminates the key error arising from estimation of LVOT cross sectional area,and is used in the assessment of native valve aortic stenosis as well as prosthetic valve stenosis [21–24].

DI MV was proposed as a potential alternative tool for the assessment of degenerative MS by Oktay et al. They demonstrated good correlation between DI MV and MVA by CE in a small cohort of patients with degenerative MS (n = 64) [20]. DI MV is derived from the ratio of LVOT TVI to the MV TVI. The advantage of this approach is that incorporating the LVOT TVI into the formula renders the DI MV relatively flow-independent. Furthermore, while DI MV is a component of the continuity equation, it does not require measurement of the LVOT diameter which is a major potential source of error in the continuity equation [6]. DI MV is expected to be lower in patients with severe MS compared to those with non severe MS. Hence, we hypothesized that DI MV may be able to differentiate severe from non severe MS in patients with rheumatic MS.

Our derivation cohort with isolated rheumatic MS showed that DI MV is significantly associated with MS severity using a reference for severe MS as adjudicated by all three of planimetry, PHT and CE methods concordantly showing MVA ≤1.5 cm^2. While each individual method of measuring MVA has its own individual limitations, we believe the requirement for all three of the planimetry, PHT and CE methods to demonstrate a concordant MVA ≤1.5 cm^2 is a robust approach to ensure that these patients truly had severe MS. Although no threshold value of DI MV had sensitivity and specificity greater than 80 %, DI MV ≤ 0.25

and DI MV $\geq$ 0.40 showed high specificity albeit with only modest sensitivity for the identification of severe and non severe MS respectively.

These threshold values were subsequently validated in the TTE and TEE validation cohorts. While it was not possible to use the CE method as a comparator in the TTE validation cohort, due to the high prevalence of regurgitant valve disease (particularly MR) which renders the CE method invalid, we still required both planimetry and PHT methods to yield MVA $\leq$1.5 cm^2 for MS to be considered severe. This reduces the risk of inaccurate classification of MS severity due to measurement error by any one single method. The validation in the TEE validation cohort is particularly significant as it validated our findings against the currently accepted gold standard method of MVA assessment [17–19]. Furthermore, the validation cohorts included patients with mixed valve disease, and subgroup analysis showed that performance of DI MV was not substantially affected by the presence of MR or AS. This extends the applicability of DI MV to a wide spectrum of patients with rheumatic MS including those with mixed valve disease including concomitant MR or AS which is a frequently encountered clinical scenario. For instance, the EuroHeart study demonstrated a 20.2 % prevalence of unspecified multiple valve pathologies, while a more recent Swedish study demonstrated that 28.3 % of patients with MS had concomitant AS, while a further 17.9 % had concomitant MR [28]. Patients with concomitant MR or AR were excluded in the study by Oktay et al. [21].

We believe that these findings suggest a role for the real-world application of DI MV in the initial assessment of patients with rheumatic heart disease and possible MS. The DI MV can be a simple yet practical way to differentiate severe from non severe MS. When DI MV is $\leq$ 0.25, MS is likely severe whereas when DI MV is $\geq$ 0.40, MS is non-severe. The required LVOT TVI and MV TVI measurements are typically routinely obtained in the echocardiographic examination of MS. It is feasible in a wide range of patients with MS including those with mixed valve disease. All in all, these points suggest a role for DI MV as a screening tool for the severity of MS where the high specificity of our identified cut-off values is advantageous. The limited sensitivity of the threshold values across the various cohorts suggests we expect to encounter some patients with intermediate DI MV values $>$ 0.25 but $<$0.40 who will not be accurately classified by DI MV alone. In real-world practice, such cases with intermediate values of DI MV $>$ 0.25 but $<$0.40 will require a detailed assessment with other echocardiographic parameters, such as conventional measures of MVA, and if necessary, subsequent evaluation with TEE if discrepancies persist. This highlights that DI MV should not be seen as replacing existing methods for assessing MVA, and further analysis would be appropriate with intermediate DI MV values $>$ 0.25 and $<$0.40 to reduce the risk of inaccurate classification of MS severity.

We found that DI MV was associated with the composite outcomes of death and MV intervention. In multivariate analysis, we found that age, DI MV and PASP were independently associated with the composite outcome. In their study that assessed DI MV in degenerative MS, Oktay et al. found that DI MV $\leq$ 0.35 showed a nonsignificant trend toward greater mortality, but did not identify any predictor with a statistically significant association with mortality [21].

Direct predictors of outcomes in rheumatic MS are not well described in the literature. Several recent cohort studies have provided some information but are limited by relatively small sample sizes and their retrospective natures. Two recent Korean studies, one focusing on all severities of MS and the second including patients with non-severe MS, found that the severity of MS and the left atrial volume index were associated with a composite outcome of death, heart failure, MV intervention and stroke [29,30]. In the study with non-severe MS, left ventricular mass index and the presence of AF were also associated with the composite outcome [29]. Another Korean study in patients with mixed MR and MS found that only a raised transmitral gradient was predictive of outcomes [31].

Our results demonstrate that a numerically smaller DI MV value, representing more anatomically severe MS, is associated with poorer clinical outcomes; this relationship is supported by recent studies in rheumatic MS [29,30]. The association between DI MV and the composite outcomes was predominantly driven by MV intervention but not all-cause mortality. This may be because the DI MV, as a surrogate for the severity of MS, may be closely linked in a direct manner to the development of symptoms. Another reason for this association is that the DI MV is calculated using the Doppler CW signal across the MV, which is also used to calculate the transmitral pressure gradient, such that patients with more severe DI MV measurements may also have higher mitral pressure gradients. The mitral pressure gradient is a key determinant of symptom status in patients with rheumatic MS and predicts symptom improvement following MV intervention such as percutaneous transmitral commisurotomy [32]. We hypothesise that these relationships between DI MV and symptom status, which is a key indication for MV intervention in patients with rheumatic MS, may explain the strong association between DI MV and MV intervention. On the other hand, the lack of significant association with death is consistent with the fact that rheumatic MS typically takes a gradual progressive course over years before becoming symptomatic (and require MV intervention) rather than rapid deterioration leading to death [33,34].

4.1. Limitations

This was a retrospective cohort study with its inherent limitations, in particular the ability to identify correlations with outcomes but not demonstrate causation. A prospective study may be valuable in studying the relationship between DI MV and outcomes in MS. We used measurements of MVA by various echocardiographic measurements (planimetry, PHT, and CE methods), as reference measurements to determine the sensitivity and specificity of DI MV. These measurements each have their own inherent limitations and sources of error which can result in inaccuracy when they are used to evaluate the accuracy of DI MV to classify severity of MS. Therefore, we required that all available methods of MVA assessment yield concordant results for patients to be considered as having severe MS which we believe is a robust approach to minimize errors contributed by any single method. We also included a TEE validation cohort, using highly accurate 3D-TEE MVA measurements, as another comparator group, though fewer patients had available TEE studies due to its semi-invasive nature. We did not study the DI MV against MVA measurements obtained by invasive cardiac catheterization and the Gorlin equation; but invasive cardiac catheterization is rarely performed in contemporary practice for assessment of MS and TTE and TEE often provide sufficient clinical information. We did not examine advanced echocardiographic measurements such as net atrioventricular compliance, left atrial reservoir strain and strain rate. These advanced parameters have been shown to have significant associations with outcomes in rheumatic MS, though they are seldom measured in clinical practice outside of a research context [35,36]. Our study did not include clinical outcomes such as heart failure or AF which may be clinically relevant. These outcomes were not studied because a substantial proportion of our patients had a prior history of heart failure or pre-existing AF. This study included only 5 patients with rheumatic MS and concomitant AR. As such, the utility of DI MV needs to be validated in this population.

5. Conclusion

Our study demonstrated that while DI MV cannot replace MVA for assessment of MS severity, it can be a useful and practical screening tool for severe MS. It can also differentiate severe from non-severe MS in situations when existing methods of MVA assessment show conflicting results. DI MV was also associated with a composite outcome of all-cause death and MV intervention. This association is mainly driven by MV intervention.

CRediT authorship contribution statement

Ryan Leow: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tony Yi-Wei Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Meei-Wah Chan:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **William KF. Kong:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kian-Keong Poh:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation. **Ivandito Kuntjoro:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Data curation. **Ching-Hui Sia:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tiong-Cheng Yeo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declarations of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2025.200366.

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