

Quantification of mitral regurgitation using transthoracic echocardiography and cardiac magnetic resonance imaging

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Both Transthoracic echocardiography (TTE) and cardiac magnetic resonance (CMR) have well-established role in mitral regurgitation (MR) quantification for optimal management strategy. We assessed the correlation between TTE and CMR in the quantification of MR. Participants with isolated MR and echocardiographic mitral regurgitant volume (RVol) ≥ 30 mL/beat were included. A consecutive sample of 30 participants (Mean age 52.7 ± 19.3 years, 50% males) was selected and referred for indirect and direct CMR quantification of mitral RVol. There was a statistically significant strong positive correlation between the echocardiographic and indirect CMR quantification of the mitral RVol ($r = 0.753$, $P < 0.001$) and a statistically significant moderate positive correlation between the echocardiographic and direct CMR quantification of the mitral RVol ($r = 0.530$, $P < 0.003$). The inter-observer reliability of the MR grade between TTE and CMR showed a statistically significant moderate agreement ($\kappa = 0.502$, $P = 0.0001$) when the observers used the echocardiographic mitral RVol for grading of MR. On the other hand, the inter-observer reliability of the MR grade between TTE and CMR showed a statistically significant faint agreement ($\kappa = 0.251$, $P = 0.024$) when the observers used the echocardiographic regurgitant fraction (RF) for grading of MR. The positive reciprocal relationship between the CMR and the TTE highlights the potential role of the CMR as a concomitant imaging tool for quantification of the mitral RVol and grading of isolated MR, especially with limited or inconclusive TTE studies. This will enhance the management strategy and improve outcomes.

Keywords

Mitral regurgitation; Echocardiography; Cardiac magnetic resonance

1. Introduction

Mitral regurgitation (MR) is a major cause of morbidity and mortality affecting 38,270 persons per 1 million US adult population [1]. Subgroup analysis of the European registry of MR (EuMiClip) data showed a 5.2% prevalence of significant MR and 70% of patients with severe primary MR had a class I indication for surgery [2]. Transthoracic echocardiography (TTE) is the standard approach for the assessment of MR. Despite its numerous technical and non-technical limitations, TTE has been recommended by the American Society of Echocardiography for the quantification of MR [3].

Cardiac magnetic resonance (CMR) is a favored diagnostic imaging technique for valvular heart disease due to its numerous features as non-ionizing radiation, excellent imaging quality, unlimited scan widows with high accuracy and reproducibility, and tissue diagnosis [4]. We wanted to evaluate the correlation between TTE and CMR in the quantification of MR and explore their complementary use for enhancing diagnostic accuracy and improving patient outcomes.

2. Methods

2.1 Study design

Our study was a 1-year cross-sectional, open-labeled, non-randomized, single cohort study conducted at a single cardiac center in a tertiary care hospital. Investigators weren't blinded to the study group. The study design was approved by the hospital ethics committee review board, all participants signed written informed consents, study procedures were carried out following the Code of Ethics of the World Medical Association (Declaration of Helsinki), all information/images were anonymized, and the privacy rights of the study participants were observed diligently.

2.2 Study participants

Study participants were patients referred to the cardiology department. They were subjected to history taking and data collection for age, gender, risk factors especially hypertension, diabetes mellitus (DM), chronic kidney disease, coronary artery disease, smoking and hyperlipidemia, nature and course of ischemic, pulmonary congestion and low cardiac output symptoms, and comprehensive clinical examination.

2.3 Study procedures

Thirty eligible participants were enrolled, consecutively assigned and allocated in a single cohort, and underwent TTE using Phillips EPIQ 7 ultrasound system for cardiology equipped with xMATRIX transducer (X5-1). Data documented with TTE included jet dimensions, vena contracta, mitral regurgitant volume (RVol) quantification by proximal isovelocity surface area (Echo_RVol), effective regurgitant orifice area, mitral regurgitant fraction (RF) deter-

Table 1. ACC/AHA guidelines for Mitral Regurgitation quantification

	Mild Grade 1	Moderate Grade 2	Moderate-Severe Grade 3	Severe Grade 4
Qualitative				
Colour Doppler jet area	Small, central jet ($< 4 \text{ cm}^2$ or $< 20\%$ LA area)	Signs of MR greater than mild present, but no criteria for severe MR.		large jet (area $\geq 40\%$ of LA area) or with a wall-impinging jet of any size, swirling in LA.
Doppler vena contracta width (mm)	< 3.0	30-49	50-69	≥ 7.0
Quantitative				
Regurgitant volume (mL)	< 30	30-44	45-59	≥ 60
Regurgitant Fraction (%)	< 30	30-39	40-49	≥ 50
Regurgitant orifice area (cm^2)	< 0.2	0.20-0.29	0.30-0.39	≥ 0.4
Additional essential criteria				
LA size				Enlarged
LV size				Enlarged

LA, left atrium; MR, mitral regurgitation.

Table 2. Cardiac Magnetic Resonance methods used in Mitral Regurgitation Quantification

Direct estimation of flow and volume by VENC *
MR = LVSV- RVSV*
MR = LVSV-AVSV
MR = LASV-AVSV

* The methods used in our study. AVSV, aortic valve stroke volume; LASV, left atrium stroke volume; LVSV, Left ventricle stroke volume; MR, mitral regurgitation; RVSV, Right ventricle stroke volume; VENC, velocity encoding.

mined by the quantitative Doppler method (Echo_RF), early diastolic mitral E wave velocity (E wave), left atrial (LA) volume, and left ventricular (LV) volume and function by the modified Simpson's biplane method. MR was categorized based on Echo_RVol and Echo_RF into mild (< 30 mL/beat), moderate (30-44 mL/beat based on Echo_RVol vs 30-39 mL/beat based on Echo_RF), moderate to severe (45-59 mL/beat based on Echo_RVol vs 40-49 mL/beat based on Echo_RF) and severe (≥ 60 mL/beat based on Echo_RVol vs ≥ 50 mL/beat based on Echo_RF) grades (Table 1) [5]. Screened participants were enrolled if they had isolated MR and Echo_RVol ≥ 30 mL/beat. Screened participants with multiple valvular heart disease, Echo_RVol < 30 mL/beat, contraindications for CMR including cardiac pacemaker or mechanical prosthesis, insulin pumps and metallic intraocular objects, incomplete or suboptimal TTE study, or pregnancy were excluded from the study.

The enrolled study participants underwent cardiac magnetic resonance (CMR) within one week for quantification of MR using Siemens Magnetom Aera 1.5T magnetic resonance imaging scanner. Data documented with CMR include indirect quantification of mitral RVol by measuring the difference between left and right ventricle stroke volumes (CMR_RVol₁) and direct quantification of mitral RVol by phase-contrast velocity mapping (CMR_RVol₂) (Table 2) (Fig. 1) [6].

2.4 End points

The study evaluated the correlation between Echo_Rvol and CMR_RVol₁, and the correlation between Echo_RVol and CMR_RVol₂. Secondary objectives included assessment of the inter-observer reliability of the MR grade between TTE and CMR.

2.5 Statistical analysis

The echocardiographic and CMR assessment outcomes were coded, and the data was analyzed with the Statistical Package for the Social Sciences software for MAC (SPSS®) version 26. Quantitative (continuous) data was expressed as means and standard deviations, while qualitative (categorical) data was expressed as medians and ranges. Parametrically distributed quantitative variables were compared with the Independent two-tailed *t*-test and correlated with Pearson's Correlation Coefficient, respectively. Pearson's Correlation Coefficient (*r*) value was interpreted as follows: 1 means perfect correlation, 0.75-1.0 is strong correlation, 0.50-0.75 is moderate correlation, 0.25-0.5 is weak correlation, and < 0.25 means no relationship. The intraclass correlation coefficient (ICC), two-way random model and absolute agreement type were used for comparison between quantitative measurements. The scale of ICC ranges from 0 to 1 where 1 represents perfect reliability with no measurement error and 0 represents no reliability. ICC Value < 0.5 indicates poor reliability, 0.5-0.75 indicates moderate reliability, 0.75-0.9 indicates good reliability and greater than 0.90 indicates excellent reliability [7]. Bland-Altman plot was used for the evaluation of bias between the means of the two modalities within 95% limits of agreement [8]. For categorial agreement, Cohen's kappa coefficient (κ) was used. Kappa values ≤ 0 means no agreement, 0.01-0.20 means none to slight agreement, 0.21-0.40 means fair agreement, 0.41-0.60 means moderate agreement, 0.61-0.80 means substantial agreement, and 0.81-1.00 means almost perfect agreement [9]. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Any comparison considered statistically significant was at $P < 0.05$ or less.

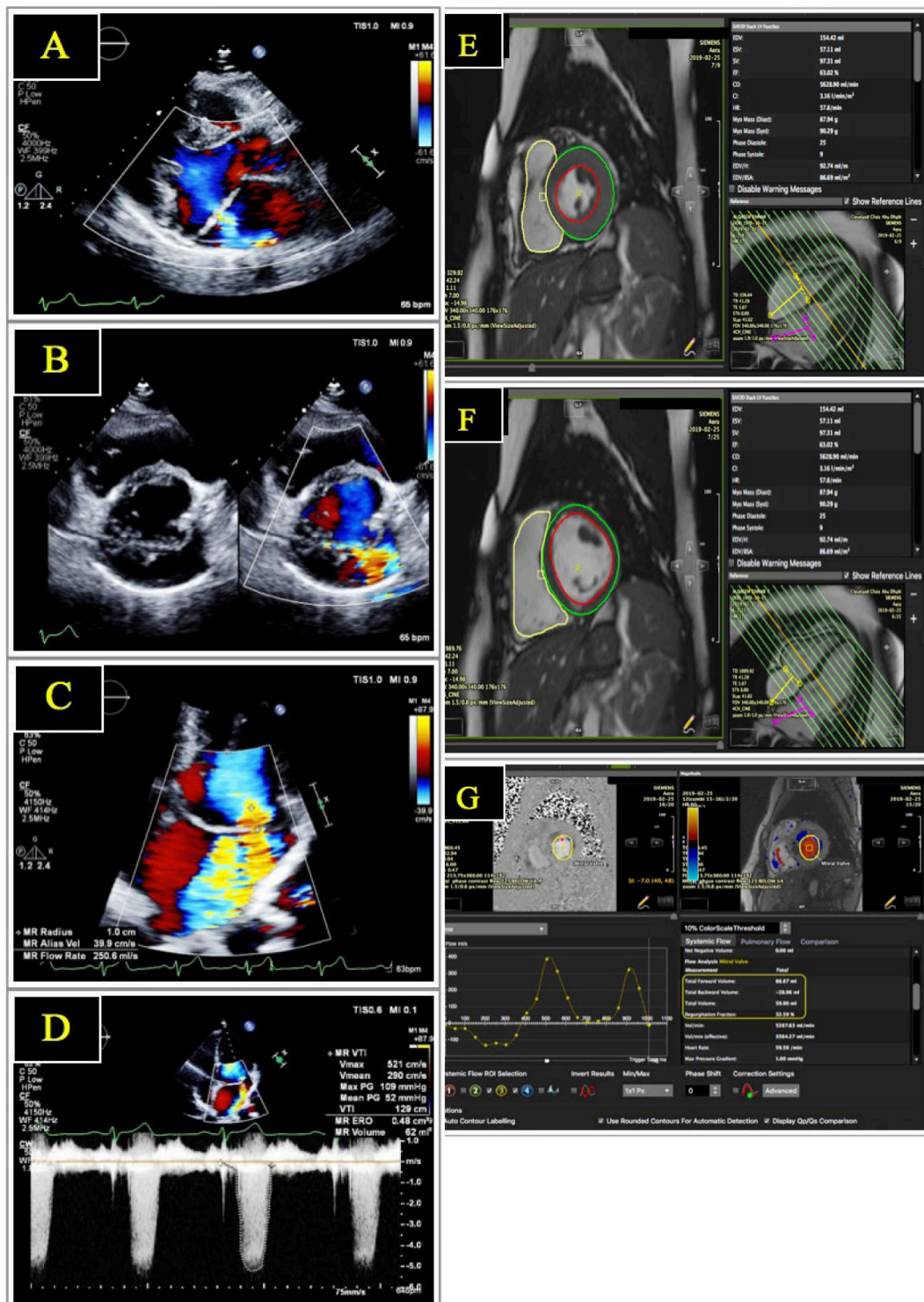


Fig. 1. Echo and CMR images of patient with severe eccentric MR. Showing severe primary MR with eccentric jet by echo (Rvol 62 mL, EROA 0.48 cm²) showing excellent correlation with CMR-Rvol₁ (Rvol 59 mL, RF 50%). And moderate correlation with CMR_Rvol₂ (Rvol 28.92 mL, RF 32%). From A to D are Transthoracic echo images showing; (A) Parasternal Long axis view showing MV bileaflets prolapse with posteriorly directed eccentric MR jet. (B) short axis view at basal LV. (C) proximal isovelocity surface area (PISA) MR with radius 1.0 cm, Nyquist limit 39.9 cm/s. (D) Continuous wave (CW) doppler showing Vmax and VTI of MR jet. Form E to G are CMR images showing. (E) Short axis slice showing LV end systolic volume. (F) Short axis slice showing LV end diastolic volume. (G) Phase contrast velocity encoding (VENC) showing total forward flow (mitral valve stroke volume = 88.87 mL), Flow reversal (CMR_Rvol₂=28.92 mL).

Table 3. Patient characteristics and demographic data (N = 30)

Age (Years)	52.7	19.3
Male	15	50.0%
Diabetes Mellitus	10	33.3%
Hypertension	14	46.6%
Hyperlipidemia	14	46.6%
Chronic Kidney Disease	10	33.3%
Coronary Artery Disease	12	40.0%
Smoker	6	20.0%
Chest pain	6	20.0%
Shortness of Breath	16	53.3%
Palpitations	5	16.6%
Echocardiography		
Mild	-	-
Moderate	17	56.6%
Mod-Sev	8	26.6%
Severe	5	16.6%
Cardiac Magnetic Resonance		
Mild	5	16.6%
Moderate	12	40.0%
Moderate-Severe	10	33.3%
Severe	3	10.0%
Mitral Regurgitation type		
Primary	12	40.0%
Secondary	18	60.0%
Jet direction		
Central	20	66.7%
Eccentric	10	33.3%
Ejection fraction		
≥ 60%	20	66.7%
< 60%	10	33.3%

Values are mean \pm SD or N and (%).

3. Results

3.1 Study participants and procedures

We recruited 30 patients from one hospital in one country from January 2019 through December 2019. The study group was balanced with regards to baseline characteristics and risk factors. The key sociodemographic feature of enrolled participants was equal gender representation (Mean age 52.7 ± 19.3 years, 50% males, 50% females). All enrolled participants completed the study and there were no withdrawals. As per TTE assessment, 56.7% had moderate MR, 26.7% had moderate-severe MR, and 16.7% had severe MR. On the other hand, 16.7% had mild MR, 40.0% had moderate MR, 33.3% had moderate to severe MR and 10% had severe MR as per CMR assessment. Primary MR was observed in 12 (40.0%) patients, secondary MR in 18 (60.0%) patients, central jet in 20 (66.7%) patients, and eccentric jet in 10 (33.3%) patients. Twenty (66.7%) patients had normal left ventricular systolic function with ejection fraction $\geq 60\%$, while 10 (33.3%) patients had left ventricular ejection fraction $< 60\%$ (Table 3).

3.2 Left ventricular volume indices

The mean left ventricle end-diastolic volume (LVEDVi) was 80.2 ± 33.5 mL/m² by TTE vs 103.1 ± 29.3 mL/m² by CMR, the mean left ventricle end-systolic volume (LVESVi) was 44.6 ± 30.5 mL/m² by TTE vs 60.8 ± 33.4 mL/m² by CMR, the mean left ventricle stroke volume (LVSVi) was 34.3 ± 15.8 mL/m² by TTE vs 42 ± 16.7 mL/m² by CMR, the mean left atrial volume (LAVi) was 45.8 ± 16.1 mL/m² by TTE vs 46.8 ± 18.1 mL/m² by CMR, and the mean left ventricle ejection fraction (LVEF) was 47 ± 19.2 % by TTE vs 44.7 ± 19.7 % by CMR, respectively. There was a statistically significant good reliability between the mean LVEDVi by TTE and the mean LVEDVi by CMR, the mean LVESVi by TTE and the mean LVESVi by CMR, the mean LVSVi by TTE and the mean LVSVi by CMR, the mean LAVi by TTE and the mean LAVi by CMR, and a statistically significant excellent reliability between the mean LVEF by TTE and the mean LVEF by CMR (ICC = 0.839, 0.888, 0.786, 0.751, and 0.956, respectively, $P \leq 0.0001$) (Table 4).

3.3 Mitral regurgitant volume

The mean mitral RVol was 45.0 ± 12.99 mL/beat by TTE quantification, 42.75 ± 12.48 mL/beat by indirect CMR quantification, and 34.23 ± 11.66 mL/beat by direct CMR quantification. There was a statistically significant strong positive correlation between Echo_RVol and CMR_RVol₁ ($r = 0.753$, $n = 30$, $P < 0.001$) (Fig. 2) and a statistically significant good reliability between Echo_RVol and CMR_RVol₁ (ICC = 0.859, 95% CI 0.706-0.932, $P \leq 0.0001$) (Table 5), a statistically significant moderate positive correlation between Echo_RVol and CMR_RVol₂ ($r = 0.530$, $n = 30$, $P < 0.003$) (Fig. 3), and statistically significant moderate reliability between Echo_RVol and CMR_RVol₂ (ICC 0.557, $P \leq 0.001$). This agreement between Echo_RVol and CMR_RVol₁ was statistically significant with excellent reliability in patients with normal EF (LVEF $\geq 60\%$) (ICC 0.942, 95% CI 0.800-0.983, $P \leq 0.0001$), but non-significant with moderate reliability in patients with low EF (LVEF $< 60\%$) (ICC 0.527, 95% CI 0.263-0.823, $P = 0.066$). Bland-Altman plot demonstrated bias of 2.24 units between the means of Echo_RVol and CMR_RVol₁ within 95% limits of agreement (95% CI 15.12-19.60) (Fig. 4).

3.4 Mitral regurgitation grade

The inter-observer reliability of the MR grade between TTE and CMR was seen in 20 (66.4%) patients showing statistically significant moderate agreement ($\kappa = 0.502$, $P = 0.0001$) when the observers used Echo_RVol for grading of MR (Table 6, Fig. 5), while the inter-observer reliability of the MR grade between TTE and CMR was seen in 15 (50%) patients showing statistically significant faint agreement ($\kappa = 0.251$, $P = 0.024$) when the observers used Echo_RF for grading of MR (Table 7, Fig. 6).

Table 4. Intraclass correlation between Echocardiography and Cardiac Magnetic Resonance for quantitative parameters

	Echo			CMR		ICC	P-value
	Mean	SD		Mean	SD		
EDVI	80.2	33.5	EDVI_CMV	103.1	29.3	0.839	< 0.0001*
ESVI	44.6	30.5	ESVI_CMV	60.8	33.4	0.888	< 0.0001*
SVI	34.3	15.8	SVI_CMV	42	16.7	0.786	< 0.0001*
EF	47	19.2	EF%_CMV	44.7	19.7	0.956	< 0.0001*
LAVI	45.8	16.1	LAVI_CMV	46.8	18.1	0.751	< 0.0001*

*Significant. EDVI, left ventricle end-diastolic volume, index; EF, LV ejection fraction; ESVI, left ventricle end-systolic volume index; LAVI, left atrium volume index; SVI, left ventricle stroke volume index.

Table 5. Intraclass correlation between Echo-RVol and CMR-RVol by indirect quantification

	Intraclass Correlation ^b	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.752 ^a	.554	.873	7.253	29	29	.000
Average Measures	.859	.706	.932	7.253	29	29	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

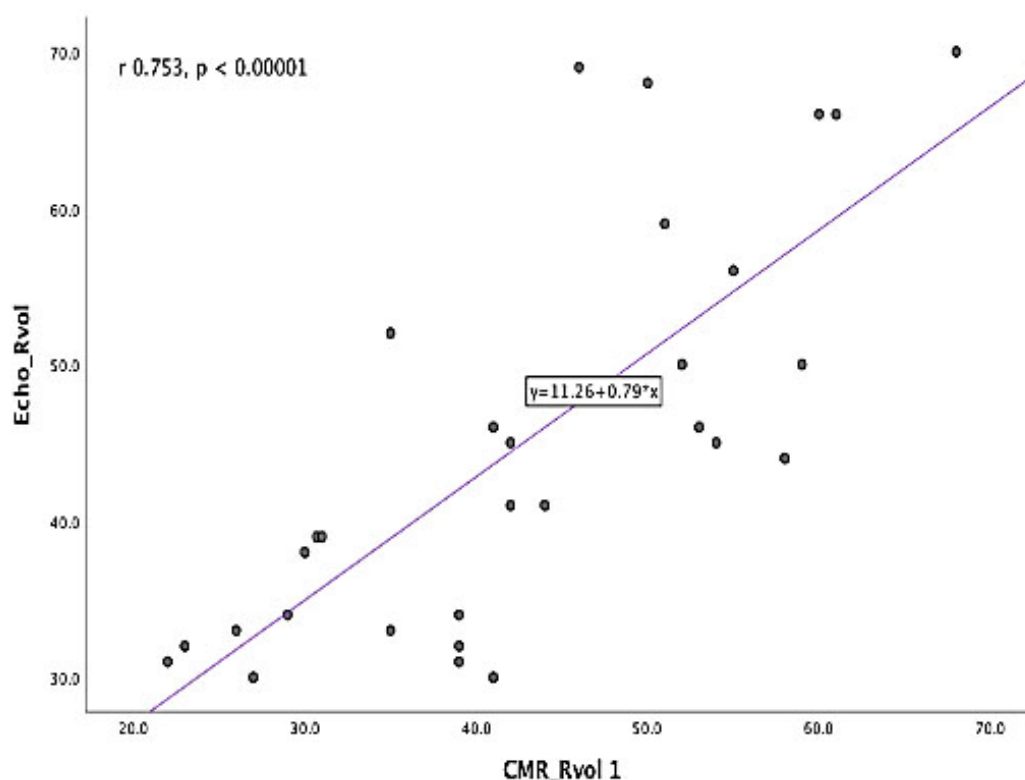


Fig. 2. The correlation between Rvol by echo vs CMR by indirect quantification. Simple Scatter plot with fit line demonstrating statistically significant strong positive correlation between echo mitral regurgitant volume (Echo_RVol) and CMR mitral regurgitant volume by indirect quantification (CMR_RVol₁) ($r = 0.753$, $P < 0.00001$).

4. Discussion

Mitral regurgitation (MR) is a major cause of morbidity and mortality worldwide. Transthoracic echocardiography (TTE) is the standard approach for assessment of MR.

Cardiac Magnetic Resonance (CMR) is a favored diagnostic imaging technique for valvular heart disease. We hypothesized that integration of TTE and CMR will enhance the diagnostic accuracy of MR and improve patient outcomes. We wanted to evaluate the correlation between TTE and CMR in

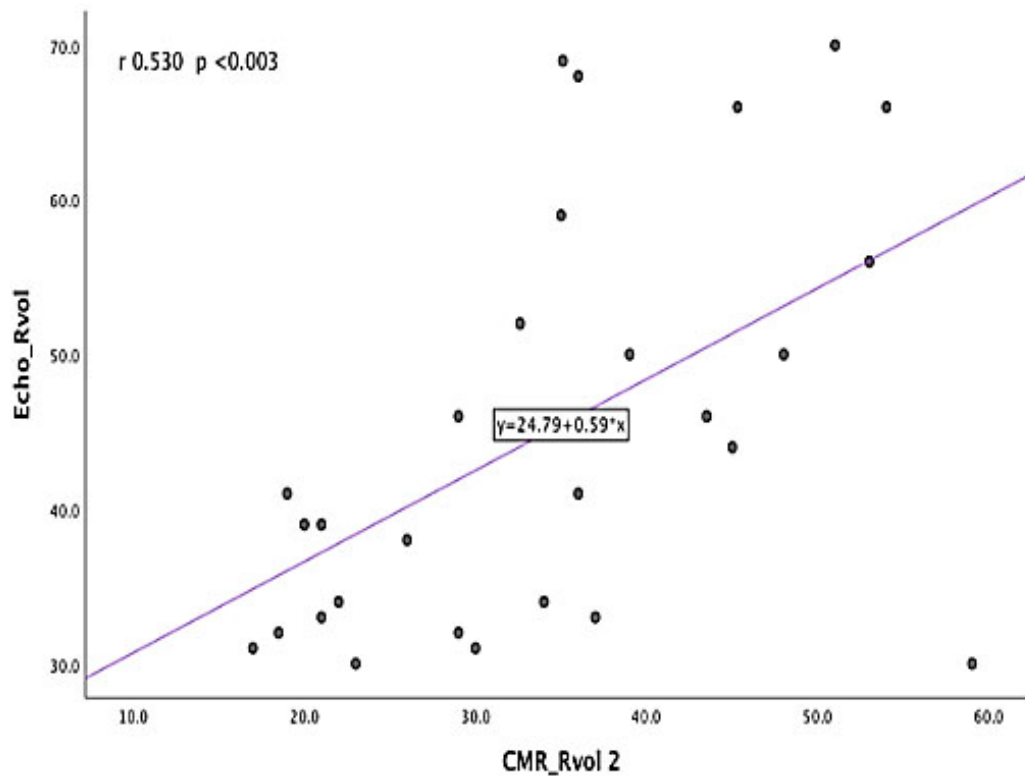


Fig. 3. The correlation between RVol by Echo vs CMR by direct quantification (velocity mapping). Simple scatter plot with fit line demonstrating positive moderate correlation between Echo-RVol and CMR-RVol by velocity mapping (CMR_RVol₂) (r 0.530, P < 0.003).

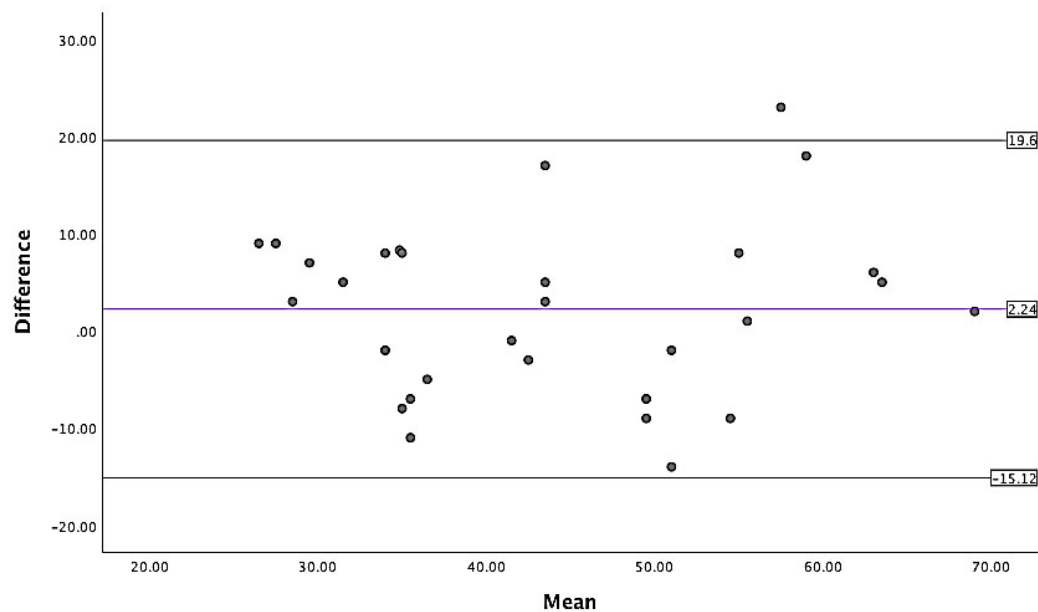


Fig. 4. Bland-Altman plot showing bias of 2.24 units between the means of RVol by Echo vs CMR by indirect quantification within 95% limits of agreement. Bland-Altman Plot demonstrating bias of 2.24 units between the means of Echo-RVol vs CMR_RVol₁ within 95% limits of agreement (95% CI 15.12-19.60).

the quantification of MR. Our 1-year cross-sectional, open-labeled, non-randomized, single cohort study revealed a statistically significant good reliability between Echo_RVol and CMR_RVol₁ by the indirect quantification (ICC = 0.859, 95%

CI 0.706-0.932, $P \leq 0.0001$). However, the integrated grading of MR by Echo_RF waived this agreement ($\kappa = 0.251$, $P = 0.024$). Sachdev, V *et al.* has reached the same conclusion, where the Echo_RVol correlated well with CMR_RVol₁ for

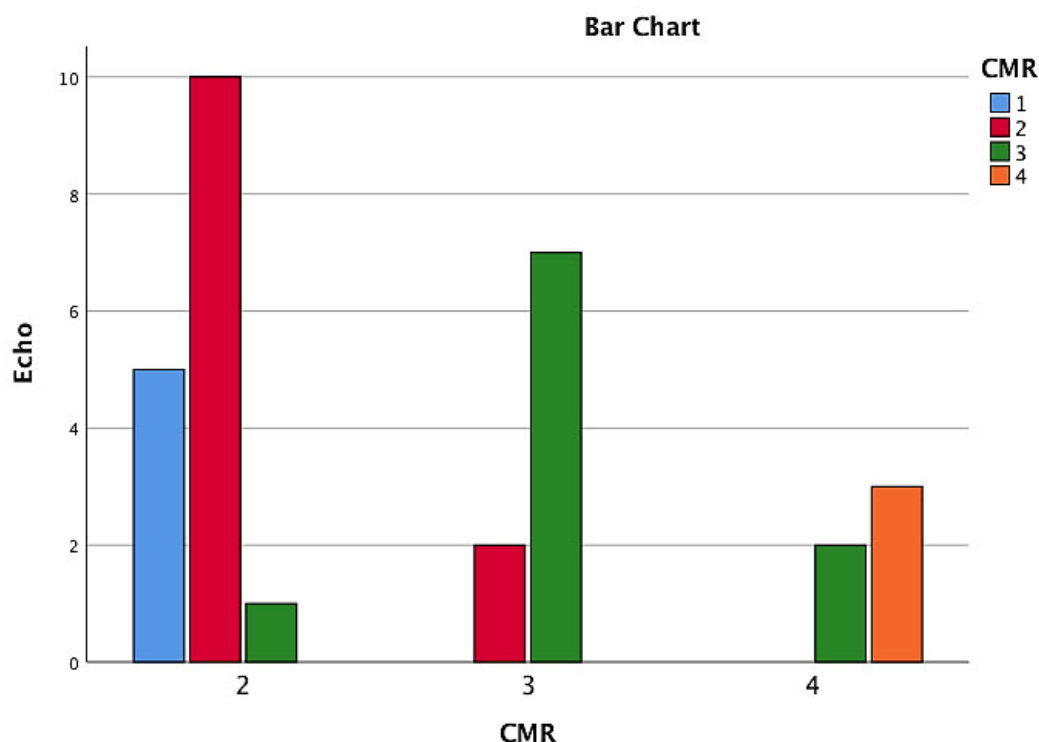


Fig. 5. Bar chart showing the patients with the same versus different MR category between echo versus CMR based on RVol. 1. Blue; Patients with mild MR, 2. Red; Moderate MR, 3. Green; Moderate to severe MR and 4. Orange; Severe MR.

Table 6. The MR categorical (grade) agreement between echo and CMR based on RVol

		CMR				Total
		1	2	3	4	
Echo	2	5	10	1	0	16
	3	0	2	7	0	9
	4	0	0	2	3	5
Total		5	12	10	3	30

Showing the comparison between Echo and CMR when only Regurgitant Volume by Echo (Echo-RVol) was used for the MR category (grade), the overall agreement improved to 20 (66.67%) patients. Yellow color indicates agreement.

Table 7. The MR Categorical (grade) agreement between echo and CMR based on RF

		CMR				Total
		1	2	3	4	
Echo	2	5	8	4	0	17
	3	0	4	4	0	8
	4	0	0	2	3	5
Total		5	12	10	3	30

Showing the comparison between Echo and CMR when the Regurgitant fraction (Echo-RF) integrated based approach was used for the MR category (grade) by Echo. the overall agreement was seen in 15 (50%) patients. Yellow color indicates agreement.

indirect quantification of MR, but the integrated assessment where regurgitant fraction (RF) was used for grading by TTE minimized the agreement between echocardiography and CMR [10]. Another study by Uretsky S, *et al.* concluded that the grading of MR severity had a significant moderate agreement between TTE and CMR in the overall cohort ($r = 0.6$; $P < 0.0001$) and a significant fair correlation between TTE and CMR in the subset of patients sent for mitral valve surgery ($r = 0.4$; $P = 0.01$). The post-surgical left ventricle reverse remodeling quantified by CMR had a significant strong correlation with the MR severity when assessed by MRI ($r = 0.85$; $P < 0.0001$) and non-significant poor correlation with the echocardiographic MR severity ($r = 0.32$; $P = 0.1$) [11]. The American society of echocardiography has

recommended RF integrated approach for quantification of MR [3]. Calculation of the RF as the ratio of the RVol to the LV stroke volume is valid for quantification of aortic regurgitation. However, the same principal doesn't apply for MR leading to quantification error. CMR has a unique ability to quantify both RVol and RF by phase-contrast velocity mapping in a single step. It is easily reproducible in patients indicated for follow up and is extremely important for quantification of atrioventricular valvular incontinence. Our study showed that CMR_RVol₂ had a moderate correlation with Echo_RVol (ICC 0.557, $P < 0.001$). The CMR direct flow quantification method downgraded the RVol (34.23 ± 11.66 mL/beat as assessed by CMR vs 45.0 ± 12.99 mL/beat

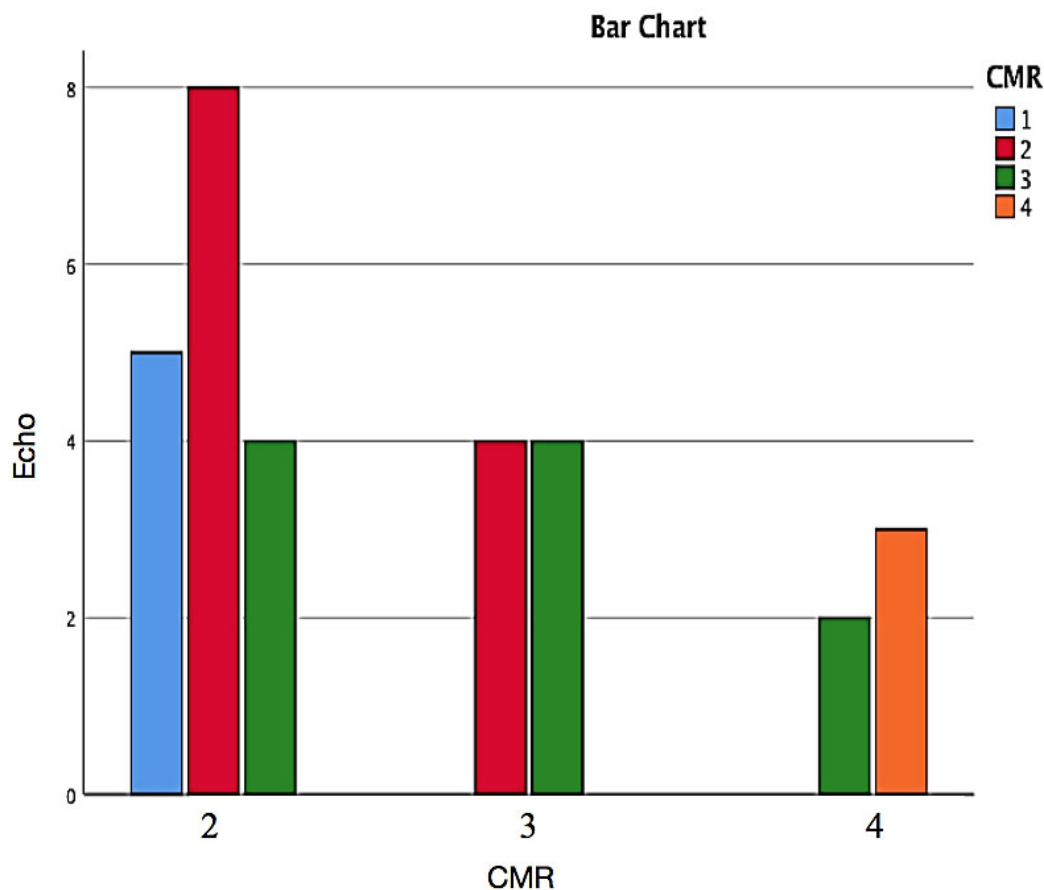


Fig. 6. Bar chart showing the patients with the same versus different MR category between echo versus CMR based on RF. 1.Blue; Patients with mild MR, 2. Red; Moderate MR, 3. Green; Moderate to severe MR and 4. Orange; Severe MR.

when assessed by TTE). Possible reasons for underestimation of the RVol by CMR include technical limitations of the CMR which led to underrepresentation of patients with moderate, moderate-severe, and severe MR, respiratory and electrical gating artifacts, and/or lower temporal resolution of the CMR flow measurement (25-45 ms) compared to the continuous wave doppler echocardiography (2 ms) which led to quantification error of the high-velocity, short duration MR jets [12]. The time-resolved multidimensional velocity encoded flow CMR (4D flow) has better quantification of the MR irrespective of the direction and/or the number of jets as the 4D can measure the jet flow with high spatial resolution in x-, y-, and z-directions simultaneously [4].

4.1 Strengths and limitations

Our study didn't have missing data allowing robust per-protocol analysis, the investigators who analyzed and reported the CMR assessment outcomes were blinded to the participants' clinical data and TTE results, and a second investigator blinded to the CMR measurements reported by the first investigator repeated them at a different time interval to evaluate the inter-observer reproducibility. On the other hand, the study has important limitations. It was a single centered study with small sample size. Being a cross-sectional study with a lack of lengthy follow up didn't allow us to in-

vestigate the chronological relationship between the TTE results, the CMR measurements, and the clinically driven outcomes.

5. Conclusions and recommendations

In our study, the positive correlation between the TTE and the CMR in quantification of mitral RVol highlights the potential role of CMR as a complementary imaging tool to TTE, especially in limited or inconclusive TTE studies. The RF by CMR is more accessible and reproducible, unlike the challenging Echo_RF. This unique feature of CMR leads to better grading and classification of MR which enhances MR management strategy and may improve patients' cardiovascular outcomes. Large prospective studies are warranted to improve the sensitivity and accuracy of the phase-contrast velocity mapping and compare CMR vs TTE regarding the measurement of cardiovascular clinical outcomes in patients with valvular heart disease, especially in asymptomatic MR patients who do not have Class I indications for surgery.

Abbreviations

bSSFP, balanced steady state free precession; CMR, cardiac magnetic resonance; CW, continuous wave doppler; Echo, echocardiography; EROA, effective regurgitant ori-

fice area; ICC, intraclass correlation coefficient; LAVi, left atrium volume index; LAEDV, left atrium end diastolic volume; LAESV, left atrium end systolic volume; LVEF, left ventricle ejection fraction; LVEsI, left ventricle end systolic volume index; LVEDi, left ventricle end diastolic volume index; LV, left ventricle; LVSV, left ventricular stroke volume; MR, mitral regurgitation; MV, mitral valve; PISA, proximal isovelocity surface area; PW, pulsed wave doppler; RF, radio frequency; RF, regurgitant fraction; RV, right ventricle; Rvol, regurgitant volume; SAX, short axis stack; SD, standard deviation; TE, echo time; TR, repetition time; VC, vena contracta; VENC, velocity encoding; VTI, velocity time integral.

Author contributions

WT did the patients recruitment, reviewed, analysed, interpreted the patient data and writing the manuscript. KA reviewed and approved the study protocol, TM helped in writing and reviewing the manuscript. HE has a major contributor in writing and reviewing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Approved by Research and Ethical committee.

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Conflict of interest

The authors declare no conflict of interest.

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