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ORIGINAL RESEARCH

Clinical and 2D/3D-Echo Cardiography Determinants of Mitral Valve Reoperation in Children With Congenital Mitral Valve Disease

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ABSTRACT

BACKGROUND Congenital mitral valve disease (CMVD) presents major challenges in its medical and surgical management.

OBJECTIVES The purpose of this study was to investigate the value of 3-dimensional echocardiography (3DE) and identify associations with MV reoperation in this setting.

METHODS All children <18 years of age who underwent MV reconstruction for CMVD in 2002 to 2018 were included. Preoperative and postoperative 2-dimensional echocardiography (2DE) and 3DE data were collected. Competing risks and Cox regression analysis were used to identify independent associations with MV reoperation. Receiver operating characteristic and decision-tree analysis were implemented for comparison of 3DE vs 2DE.

RESULTS A total of 206 children underwent MV reconstruction for CMVD (mitral stenosis, n = 105, mitral regurgitation [MR], n = 75; mixed disease, n = 26); 64 (31%) required MV reoperation. Variables independently associated with MV reoperation were age <1 year (HR: 2.65; 95% CI: 1.13-6.21), tethered leaflets (HR: 2.00; 95% CI: 1.05-3.82), ≥ moderate 2DE postoperative MR (HR: 4.26; 95% CI: 2.45-7.40), changes in 3D-effective orifice area (3D-EOA) and in 3D-vena contracta regurgitant area (3D-VCRA). Changes in 3D-EOA and 3D-VCRA were more strongly associated with MV reoperation than changes in mean gradients (area under the curve [AUC]: 0.847 vs AUC: 0.676, $P = 0.006$) and 2D-VCRA (AUC: 0.969 vs AUC: 0.720, $P = 0.012$), respectively. Decision-tree analysis found that a <30% increase in 3D-EOA had 80% accuracy (HR = 8.50; 95% CI: 2.9-25.1) and a <40% decrease in 3D-VCRA had 93% accuracy (HR: 22.50; 95% CI: 2.9-175) in discriminating MV reoperation for stenotic and regurgitant MV, respectively.

CONCLUSIONS Age <1 year, tethered leaflets, 2DE postoperative MR, changes in 3D-EOA and 3D-VCRA were all independently associated with MV reoperation. 3DE parameters showed a stronger association than 2DE. 3DE-based decision-tree algorithms may help prognostication and serve as a support tool for clinical decision-making. (JACC Adv 2024;3:101081) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

2DE = 2-dimensional echocardiography

3DE = 3-dimensional echocardiography

AUC = area under the curve

AV = atrioventricular

CHD = congenital heart disease

CMVD = congenital mitral valve disease

EOA = effective orifice area

ICC = intraclass correlation coefficient

MD = mixed disease

MR = mitral regurgitation

MS = mitral stenosis

MV = mitral valve

VCRA = vena contracta regurgitant area

Congenital mitral valve disease (CMVD) is a rare and heterogenous congenital heart disease (CHD) with variable anatomic characteristics and prognosis. The disease may affect multiple segments of the valve apparatus including the supravalvar region, annulus, leaflets, commissures, as well as the subvalvar region.[1,2] Despite medical management, children with CMVD often require catheter-based or surgical interventions.[3] MV repair is generally preferred over MV replacement due to its ability to preserve the subvalvar apparatus and its function, conserve the overall ventricular geometry, and allow tissue growth over time.[4-7] However, studies have shown that surgical results have been burdened by a non-negligible proportion of reoperation for either MV reconstruction or replacement.[3,5,8]

The identification of factors possibly associated with higher risk of reoperation may help guide risk stratification and management in this peculiar cohort of patients. In the last decades, studies have tried to identify predictors of MV reoperation in patients with CMVD.[5,8-10] However, often these studies were affected by small sample sizes, or included patients with marked heterogeneity in their baseline MV pathology.[7,9] Few studies have addressed the value of echocardiography techniques to predict MV reinterventions.[9,10]

Traditionally, cardiologists and cardiac surgeons have relied on 2D-echocardiography (2DE) for monitoring and guiding the clinical management in these patients. Three-dimensional echocardiography (3DE) provides the simultaneous assessment of the spatial relationship of the leaflets, chordae and papillary muscles, and thus more accurate and reliable measurements,[11-13] which have the potential to aid surgical planning.[14] To date, most reports assessing the benefit of 3DE in cardiac diseases have been conducted in adult patients.[11,15,16] The use of 3DE in children with CHD has been reported only for specific settings, like the evaluation of atrioventricular (AV) septal defects status post repair[17,18] or the assessment of the tricuspid valve in children with hypoplastic left heart syndrome.[19]

The main purpose of this study was to investigate associations between clinical and echocardiographic variables and MV reoperation in a large cohort of pediatric patients with CMVD. In addition to traditional patient demographics, anatomic, and clinical characteristics, we sought to assess associations between 3DE measurements and MV reoperation and to investigate the relative performance of the 3DE compared to the 2DE in this setting. Finally, we aimed to develop decision-tree algorithms for patients' prognostication to serve as a support tool for clinicians in the clinical decision-making.

MATERIAL AND METHODS

PATIENTS. The Cardiovascular Surgical Department database at Boston Children's Hospital (Boston, Massachusetts, USA) was searched for all patients <18 years of age who underwent MV surgery between January 2002 and December 2018. The Institutional Review Board at Boston Children's Hospital approved the study (IRB-P00002922 and IRB-P00023266).

Patients with hypoplastic left heart syndrome who underwent single ventricle palliation, patients with AV canal defects, AV discordance, and those with connective tissue disorders were excluded. Patients were subdivided into 3 subgroups according to the type of MV disease as follows: 1) mitral stenosis (MS) group: patients with a Doppler mean gradient >5 mm Hg and none or trivial mitral regurgitation (MR); 2) MR group: patients with a mean gradient <5 mm Hg and at least moderate MR; and 3) mixed disease (MD) group: patients with a mean gradient >5 mm Hg and at least moderate MR. Anatomical characteristics of the MV and surgical techniques were determined based on the description of the MV and the operation in the surgical report, as detailed in the Supplemental Methods.

OUTCOMES. The primary outcome measure was time to MV reoperation. Secondary outcome measures were need for MV replacement and death at any time to the last follow-up.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ECHOCARDIOGRAPHIC MEASUREMENTS. Echocardiographic measurements were performed preoperatively (within 7 days before surgery) and postoperatively either at hospital discharge or at 10 days after surgery, whichever came first.

2DE measurements. Severity of MR was extracted from the echocardiographic reports, which were generated by different echocardiographers. MR was qualitatively graded as trivial, mild, moderate, and severe. Doppler mean gradients and mitral 2D-vena contracta regurgitant area (VCRA) were calculated by 2 independent investigators. The severity of MS was graded as follows: trivial: <3 mm Hg; mild: 3 to 5 mm Hg; moderate: >5 to 10 mm Hg; and severe: >10 mm Hg. The 2D-VCRA was measured using the equation of an ellipse: $A = \pi \times a \times b$. The diameters were measured from corresponding orthogonal planes: diameter "a" from the right/left plane (apical view) and diameter "b" from the anterior/posterior plane (long-axis parasternal view).

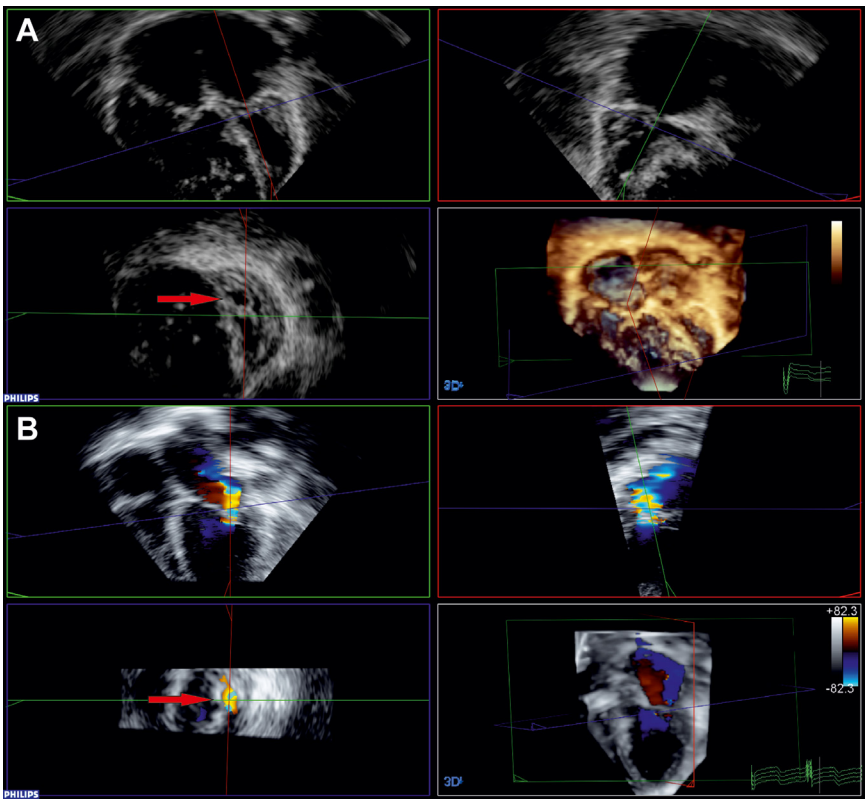
3DE measurements. Electrocardiographic-gated full-volume 3DE acquisitions were performed using a 5-1 and a 7-2 MHz matrix-array transthoracic probe (Supplemental Methods) and a 3DE ultrasound system (SONOS 7500 and iE33, Philips Medical Systems, Bothwell, WA). Full-volume 3DE data were acquired from the apical 4-chamber view. Analyses were performed with a dedicated software (Q-lab 6.0, Philips Medical Systems). 3D multi-planar imaging was used to measure the corresponding annulus, 3D-effective orifice area (EOA), and 3D-VCRA (**Figures 1A and 1B**). Based on 2 orthogonal long-axis planes, a corresponding short-axis plane was chosen to appropriately trace the MV annulus area, 3D-EOA, and 3D-VCRA (**Figures 1A and 1B**, Supplemental Methods).

STATISTICAL ANALYSIS. Demographic and anatomic characteristics are summarized using frequencies and percentages for categorical data, median (IQR) for continuous data. Paired *t*-test was used to assess variation of echocardiographic parameters over time (preoperatively and postoperatively). The Kaplan-Meier estimator was used to compute freedom from MV reoperation, MV replacement, and death at 1, 3, and 5 years after the first MV operation and 95% CIs. Inter-rater and intra rater agreement of 3DE measurements were tested using intraclass correlation coefficients (ICC) based on a 2-way mixed effects modeling, with reliability categories defined as follows: ICC <0.50 poor, 0.50 to 0.75 moderate, 0.75 to 0.90 good, >0.90 excellent.

Univariate and multivariable competing risks regression analysis using Fine-Gray modeling were used to identify significant associations between demographic, clinical, and 2DE variables and MV reoperation, accounting for mortality prior to reoperation as a competing risk event.[20,21] Preoperative variables included in the model were age, weight, sex, type of disease (MS, MR, MD), pulmonary hypertension, thickened and tethered leaflets, presence of endocardial fibroelastosis, year of surgery; postoperative factors included ≥ moderate MR, ≥ moderate MS, and 2D-VCRA. All factors except for the 2D-VCRA (due to limited sample of patients with 2D-VCRA data) were included in the multivariable model. Cumulative incidence functions were constructed overall and for diagnostic subgroups for independently associated variables using Nelson-Aalen estimators. To better investigate any independent associations with MV reoperation resulted from this model, the same model was reproduced for the subgroups of patients with MS (including MD) and MR (including MD). 3DE measurements were analyzed using univariate and multivariable time-to-event Cox proportional hazards regression analysis, for the MS (including MD) and the MR (including MD) populations separately. Factors judged to be the most clinically meaningful and less collinear to each other based on variance inflation factors analysis (variance inflation factor <5) were included. The proportional subdistribution hazard assumption was tested using Schoenfeld residuals[22] and the Grambsch-Therneau test. Results are presented as adjusted HRs and 95% CIs.

The prognostic value of 2DE vs 3DE measurements was assessed by the area under the curve (AUC) of the receiver operating characteristic curves, which were compared using the paired-DeLong test.[23] Classification and regression tree analysis was implemented to determine the optimal cut-points for 3DE measurements in discriminating MV reoperation (*rpart* package, R). Results from decision-tree analysis are presented with sensitivity, specificity, positive predictive value and negative predictive value, and accuracy of the optimized predictive cutoff thresholds. Bootstrap validation was used to evaluate the internal validity and model performance (Supplemental Methods). Statistical analyses were performed using Stata (version 16.0, StataCorp LLC) and R (version

FIGURE 1 Measurement of 3D Effective Orifice Area and 3D Vena Contracta Regurgitant Area



Multiplanar reconstruction was used to locate the optimal cross-sectional plane to determine the annulus area, 3D-EOA (A) and 3D-VCRA (B). The 3D-EOA was defined as the smallest orifice of the MV inflow. The 3D-VCRA corresponded to the cross-sectional area of the color Doppler jet at valve coaptation. (A) For 3D-EOA measurement, the frame during diastolic opening with the largest opening was chosen and the MV was aligned in 2 long-axis orthogonal planes. A cross-sectional plane (blue) was set at the smallest orifice to allow for 3D-EOA circumference planimetry. (B) For 3D-VCRA measurement, the longitudinal planes were adjusted to best visualize the regurgitant jet, allowing for placement of the cross-sectional plane at the largest circumference; 3D-VCRA was then measured before jet dispersion in orthogonal imaging planes. 3D-EOA = 3D effective orifice area; 3D-VCRA = 3D vena contracta regurgitant area.

3.4.3, R Foundation for Statistical Computing). A 2-tailed alpha level of 0.05 was considered statistically significant.

RESULTS

DEMOGRAPHIC, ANATOMIC MV CHARACTERISTICS, AND SURGICAL TECHNIQUES. A total of 206 patients (48% female) underwent MV surgery during the study period. A total of 105 patients (51%) had MS, 75 (36%) MR, and 26 (13%) MD. Eight percent were neonates, 47% were infants. The median age at the initial MV operation was 17 months (IQR: 5-56 months), the median weight was 9.1 kg (IQR: 5-16.7 kg). Details of the MV pathology, assigned to the categories of MS, MR, and MD, are shown in **Table 1**. At the time of the initial operation, MD patients were younger (median age 5 months) and smaller in weight (median weight 5.1 kg); MR patients were older (median age 48 months) and weighed more (median weight 13.7 kg) (**Table 1**). Median follow-up for the total cohort was 60 months (IQR: 18-108 months). Details of valve repair are shown in Supplemental Table 1.

MV REOPERATION AND REPLACEMENT. Sixty-four patients (31%) required MV reoperation at a median time of 9 months after the first operation (IQR: 0.4-39 months). Thirty-three (16%) patients required more than one MV reoperation. Twenty-six (12.6%)

TABLE 1 Patients' Baseline Demographic and Anatomical Characteristics

	Total Cohort (N = 206)	Mitral Stenosis (n = 105)	Mitral Regurgitation (n = 75)	Mixed Disease (n = 26)
Demographics				
Age, mo	17.3 (4.6-56)	11.9 (5.3-43.7)	47.7 (5.3-72.9)	4.6 (1.4-21.2)
Weight, kg	9.1 (5-16.7)	8.4 (5.4-13.2)	13.7 (5.2-19.6)	5.1 (3.3-11.4)
Follow-up, mo	59.4 (18.3-108.4)	63 (15.3-115.7)	55.2 (16.8-87.4)	76.8 (27.4-108.4)
Anatomical characteristics				
Double orifice mitral valve	13 (6.3%)	8 (7.6%)	3 (4%)	2 (7.7%)
Annular dilatation	50 (24.3%)	4 (3.8%)	39 (52%)	7 (26.9%)
Cleft leaflet	46 (22.3%)	0 (0%)	39 (52%)	7 (26.9%)
Elongated chordae	10 (4.9%)	0 (0%)	10 (13.3%)	0 (0%)
Shortened chordae	76 (36.9%)	47 (44.8%)	17 (22.7%)	12 (46.2%)
Absent chordae	14 (6.8%)	6 (5.7%)	4 (5.3%)	4 (15.4%)
Fused/closely spaced chordae	45 (21.8%)	37 (35.2%)	3 (4%)	5 (19.2%)
Secondary/abnormal chordae	84 (41.0%)	39 (37.1%)	26 (34.7%)	17 (65.4%)
Commissural fusion	30 (14.6%)	26 (24.8%)	0 (0%)	4 (15.4%)
Hammock valve (mitral arcade)	22 (10.7%)	12 (11.4%)	3 (4%)	7 (26.9%)
Stenosing mitral membrane	65 (31.6%)	62 (59.0%)	0 (0%)	3 (11.5%)
Endocardial fibroelastosis	62 (30.1%)	46 (43.8%)	8 (10.7%)	8 (30.8%)
Single dominant papillary muscle	27 (13.1%)	22 (21.0%)	4 (4%)	1 (3.8%)
Prolapse of the anterior leaflet	51 (24.8%)	5 (4.8%)	35 (46.7%)	11 (42.3%)
Thickened leaflets	110 (53.4%)	64 (61.0%)	30 (40.0%)	16 (61.5%)
Tethered leaflets	115 (55.8%)	58 (55.2%)	34 (45.3%)	23 (88.5%)
Tethered papillary muscles	94 (45.6%)	51 (48.6%)	23 (30.7%)	20 (76.9%)
Closely spaced papillary muscles	34 (16.5%)	28 (26.7%)	0 (0%)	6 (23.1%)

Values are median (IQR) or n (%).

required a MV replacement, at a median time of 46 months since the first operation (IQR: 0.9-18 months). Overall freedom from MV reoperation was 79.1% at 1 year (95% CI: 72.4%-84.4%; n = 132), 73.9% at 3 years (95% CI: 66.6%-79.8%; n = 97), and 66% at 5 years (95% CI: 57.7%-73%; n = 64). Thirty-six patients who underwent reoperation had MS (34% of MS), 16 MR (21% of MR), and 12 MD (46% of MD). Overall freedom from MV replacement was 89.9% at 1 year (95% CI: 84.4%-93.5%; n = 150), 87.9% at 3 years (95% CI: 82%-91.9%; n = 114), and 85.4% at 5 years (95% CI: 78.9%-90%; n = 82). Seventeen patients who underwent MV replacement had MS (16% of MS), 4 MR (5% of MR), and 5 MD (19% of MD).

MORTALITY. At a median follow-up of 60 months (IQR: 18-108 months), 13 (6%) patients did not survive. Death occurred at a median of 15 months (IQR: 2-42 months) after the first MV operation. The highest mortality rate was observed in MD patients (4/26, 15%), while the lowest was reported in MR patients (2/75, 3%). There was one perioperative/early death (<30 days) in 2005. The overall survival was 97.2% at 1 year (95% CI: 93.3%-98.8%; n = 164), 94.7% at 3 years (95% CI: 90%-97.2%; n = 131), and 93.9% at 5 years (95% CI: 88.9%-96.7%; n = 98).

ASSOCIATION OF DEMOGRAPHIC, ANATOMIC, AND 2DE VARIABLES WITH MV REOPERATION. At univariate competing risks regression analysis, age <1 year, MD, tethered leaflets, and ≥ moderate postoperative MR or MS were found to be associated with MV reoperation (Table 2). Multivariable modeling confirmed that age <1 year (adjusted HR: 2.65; 95% CI: 1.13-6.21), tethered leaflets (adjusted HR: 2.00; 95% CI: 1.05-3.82), and a qualitatively ≥ moderate postoperative MR (adjusted HR: 4.26; 95% CI: 2.45-7.40) (Figure 2A) were independently associated with MV reoperation. When stratifying for type of MV disease, ≥moderate postoperative MR was confirmed to be independently associated in both patients with stenotic MV (Figure 2B) (adjusted HR: 3.21; 95% CI: 1.73-6.00) and patients with regurgitant MV (Figure 2C) (adjusted HR: 7.38; 95% CI: 3.46-15.70).

ASSOCIATION BETWEEN 3DE VARIABLES AND MV REOPERATION. Videos 1 and 2 show examples of 3DE in 2 patients with congenital MS and MR, respectively. Eighty-six out of 206 patients (42%) had preoperative and postoperative 3DE data available. For stenotic valves, the 3D-EOA significantly increased after MV reoperation, from 0.91 ± 0.55 cm^2/m^2 to

TABLE 2 Univariate and Multivariable Competing Risks Analysis to Identify Predictors of Mitral Valve Reoperation

		Univariate Analysis			Multivariable Analysis		
	N	HR	(95% CI)	*P* Value	Adjusted HR	(95% CI)	*P* Value
Baseline and preoperative characteristics							
Age <1 y	200	3.26	(1.92-5.52)	**<0.001**[a]	2.65	(1.13-6.21)	**0.025**[a]
Weight (kg)	206	0.96	(0.91-1.01)	0.076	0.99	(0.96-1.04)	0.726
Biological sex	195						
Female		Reference	.	.	Reference	.	.
Male		1.18	(0.71-1.95)	0.524	1.21	(0.70-2.10)	0.494
Type of disease	206						
Mitral stenosis		1.71	(0.94-3.14)	0.081	1.13	(0.56-2.28)	0.726
Mitral regurgitation		Reference	.	.	Reference	.	.
Mixed		2.57	(1.16-5.71)	**0.020**[a]	1.29	(0.50-3.31)	0.600
Pulmonary hypertension	195	1.43	(0.87-2.35)	0.159	0.87	(0.49-1.56)	0.646
Thickened leaflets	206	1.22	(0.74-2.00)	0.435	1.2	(0.64-2.27)	0.570
Tethered leaflets	206	2.11	(1.23-3.61)	**0.007**[a]	2.0	(1.05-3.82)	**0.035**[a]
Endocardial fibroelastosis	205	1.16	(0.69-1.95)	0.583	0.71	(0.40-1.29)	0.263
Year of surgery	206	1.02	(0.96-1.09)	0.472	1.03	(0.95-1.12)	0.443
Postoperative imaging on 2D echo							
2D moderate or greater MR postop	193	5.2	(3.07-8.80)	**<0.001**[a]	4.26	(2.45-7.40)	**<0.001**[a]
2D moderate or greater MS postop	201	2.03	(1.18-3.46)	**0.010**[a]	1.67	(0.94-2.97)	0.082
2D VCRA	78	1.11	(0.99-1.24)	0.068		-	

Competing risks modeling was computed using the Fine and Gray model, with mortality prior to reoperation as the competing event. All the factors assessed at the univariate analysis (left) were included in the multivariable model, except for 2D VCRA, which was excluded due to the small sample size of patients assessed with this approach. Multivariable model: n = 183 patients, 57 of whom underwent MV reoperation. [a]Statistically significant.

MR = mitral regurgitation; MS = mitral stenosis; VCRA = vena contracta regurgitant area.

1.44 ± 0.69 cm^2/m^2 ($P < 0.001$). 3D-VCRA trended to increase from 0.93 ± 1.50 cm^2/m^2 to 1.49 ± 2.07 cm^2/m^2, although not significantly ($P = 0.143$). On univariate analysis, preoperative 3D-EOA, early changes in 3D-EOA and 3D-VCRA, and size of the postoperative 3D-VCRA were positively associated with MV reoperation. On multivariable analysis, early changes in 3D-EOA and 3D-VCRA were confirmed to be independently associated with MV reoperation (Table 3) (3D-EOA: adjusted HR: 0.24; 95% CI: 0.06-0.9; and 3D-VCRA: adjusted HR: 2.53; 95% CI: 1.15-5.6). For regurgitant valves, the 3D-VCRA significantly decreased from 2.22 ± 2.26 cm^2/m^2 to 1.46 ± 1.94 cm^2/m^2 ($P = 0.017$), 3D-EOA significantly decreased from 2.91 ± 1.86 cm^2/m^2 to 1.63 ± 0.73 cm^2/m^2 ($P = 0.005$), and the annuli significantly decreased from 7.53 ± 3.45 cm^2/m^2 to 4.53 ± 1.85 cm^2/m^2 ($P < 0.001$). Univariate analysis showed that the size of the preoperative 3D-VCRA, size of the postoperative 3D-VCRA, early changes in 3D-VCRA, and preoperative annulus were positively associated with MV reoperation. On multivariable analysis, early changes in 3D-VCRA were confirmed to be independently associated with MV reoperation (Table 3) (adjusted HR: 11.5; 95% CI: 3.01-44.5).

INTER- AND INTRA-RATER AGREEMENT OF 3DE MEASUREMENTS. The inter-rater agreement was good for 3D-EOA (ICC = 0.75), and excellent for both the 3D-VCRA and annulus area (ICC = 0.93 and ICC = 0.98, respectively). Intra-rater reliability was excellent for all parameters (EAO: ICC = 0.92; 3D-VCRA: ICC = 0.97; annulus area: ICC = 0.99).

COMPARISON OF 2DE VS 3DE MEASUREMENTS. The Central Illustration and Table 4 showed the comparison of 3DE vs 2DE parameters. When considering stenotic valves, early changes in 3D-EOA were found to have a stronger association with MV reoperation than 2DE early changes in mean gradients (AUC: 0.847 [95% CI: 0.723-0.970] vs 0.676 [95% CI: 0. 508-0.844], respectively; DeLong test $P = 0.006$) (Central Illustration, upper panel, left image). For regurgitant valves, early changes in 3D-VCRA were found to have a stronger association with MV reoperation than 2DE qualitative postoperative MR (AUC = 0.969 [95% CI:

0.916-0.999] vs 0.751 [95% CI: 0.642-0.860], respectively; DeLong test $P < 0.001$). Additionally, early changes in 3D-VCRA had a significantly stronger association with MV reoperation than early changes in 2D-VCRA (AUC = 0.969 [95% CI: 0.916-0.999] vs 0.720 [95% CI: 0.424-0.903], DeLong test $P = 0.012$) (**Central Illustration**, upper panel, right image).

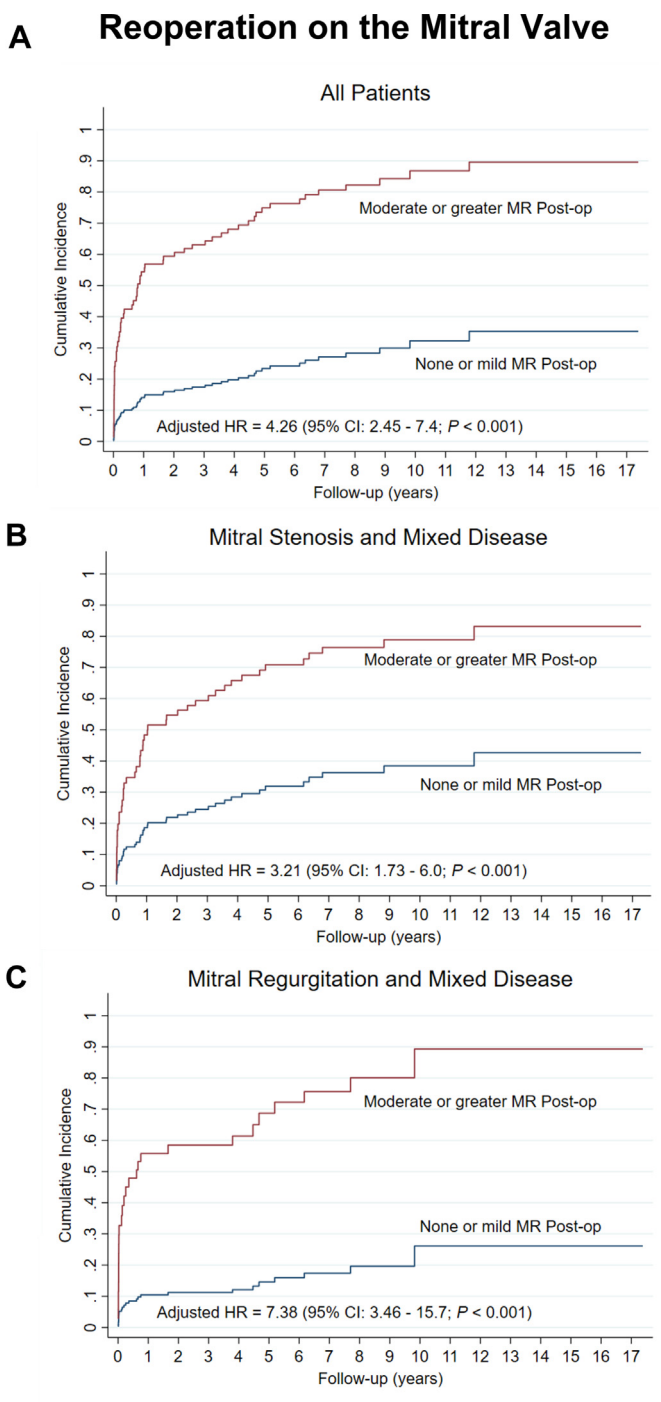
DECISION-TREE ALGORITHMS. Decision-tree algorithms were computed as a support tool for clinical decision-making (**Central Illustration**, lower panel). Sensitivity, specificity, positive predictive value, and negative predictive value are reported in **Table 4**. For stenotic valves, an increase in 3D-EOA by <30% leads to 92% risk of MV reoperation (accuracy 80%; HR: 8.50; 95% CI: 2.90-25.1; $P < 0.001$) (**Central Illustration**, lower panel, left image). For regurgitant valves, a decrease in 3D-VCRA <40% is associated with 93% risk of MV reoperation (accuracy 93%; HR: 22.50; 95% CI: 2.90-175.00; $P = 0.003$) (**Central Illustration**, lower panel, right image). Bootstrap validation demonstrated excellent internal validity and model performance (Supplemental Results).

DISCUSSION

This single-center study, which involved a large cohort of young pediatric patients undergoing MV surgery for CMVD, showed a low mortality at a median follow-up of 5 years. However, 31% of patients required a MV reoperation, and 12% requiring a subsequent MV replacement. These important surgical findings prompted investigation of associations between clinical and echocardiographic variables and MV reoperation. We showed that age <1 year, presence of tethered leaflets, evidence of moderate or greater postoperative MR on 2DE, as well as early changes in 3D-EOA and 3D-VCRA were all independently associated with MV reoperation. Importantly, when 2DE and 3DE were compared in terms of their performance to discriminate MV reoperation, certain 3DE parameters were found to have significantly higher prognostic values compared to 2DE. Based on these findings, decision-tree algorithms were developed to inform patient's prognostication, with the aim to improve assessment and help clinical decision-making (**Central Illustration**).

The fact that younger patients, in particular patients <1 year of age, are at increased risk for MV reoperation was previously reported for smaller cohorts,[5,7,8,10,24] and further confirmed in our study. Additionally, in terms of baseline MV morphology, our study showed that patients with tethered and restricted leaflets are at increased risk of MV reoperation. This is a new finding compared to what was

FIGURE 2 Competing Risk Analysis Cumulative Incidence Curves for Mitral Valve Reoperation According to Evidence of Moderate or Greater Postoperative Mitral Regurgitation by 2D Echocardiography



(A) The risk of MV reoperation was significantly higher in patients with ≥ postoperative MR (adjusted HR: 4.26; 95% CI: 2.45-7.4). (B, C) This association persisted for each baseline anatomic disease group (MS + MD patients: adjusted HR: 3.21; 95% CI: 1.73-6.0; MR + MD patients: adjusted HR: 7.38; 95% CI: 3.46-15.7). Multivariable models were adjusted for demographic, anatomic, and clinical characteristics shown in **Table 2**.
MD = mixed disease; MR = mitral regurgitation; MS = mitral stenosis.

TABLE 3 Univariate and Multivariable Cox Regression Analysis of Mitral Valve Reoperation Using 3D Echo Variables

	Univariate Cox Analysis				Multivariable Cox Analysis		
3D Echo Variable	N	HR	(95% CI)	*P* Value	Adjusted HR	(95% CI)	*P* Value
Mitral stenosis and mixed disease patients							
Size of 3D-EOA preoperatively	50	2.79	(1.48-5.25)	**0.002**[a]			
Size of 3D-EOA postoperatively	49	0.69	(0.35-1.36)	0.283			
Change of the 3D-EOA	39	0.27	(0.12-0.59)	**0.001**[a]	0.24	(0.06-0.9)	**0.034**[a]
Size of 3D-VCRA postoperatively	25	1.42	(1.06-1.90)	**0.018**[a]			
Change of 3D-VCRA	18	2.52	(1.16-5.48)	**0.020**[a]	2.53	(1.15-5.6)	**0.021**[a]
Mitral regurgitation and mixed disease patients							
Size of 3D-EOA postoperatively	30	0.80	(0.39-1.64)	0.536			
Change of 3D-EOA	30	0.96	(0.32-2.82)	0.930			
Size of 3D-VCRA preoperatively	38	1.81	(1.19-2.74)	**0.005**[a]			
Size of 3D-VCRA postoperatively	30	3.15	(1.86-5.36)	**<0.001**[a]			
Change of 3D-VCRA	30	15.7	(4.65-53.00)	**<0.001**[a]	11.5	(3.01-44.5)	**<0.001**[a]
Size of the 3D annulus preoperatively	45	1.03	(0.91-1.17)	0.649			
Size of the 3D annulus postoperatively	30	1.16	(0.98-1.39)	0.086			
Change in 3D annulus size	29	4.24	(1.00-18.3)	**0.050**[a]	1.95	(0.29-13.6)	0.511

Factors found to be statistically significant at univariate analysis were included in the multivariable model. Multivariable analysis for patients with mitral stenosis and mixed disease: n = 18 (no. of events = 11). Multivariable analysis for patients with mitral regurgitation and mixed disease: n = 25 (no. of events = 13). [a]Statistically significant.

3D-EOA = 3D effective orifice area; 3D-VCRA = 3D vena contracta regurgitant area.

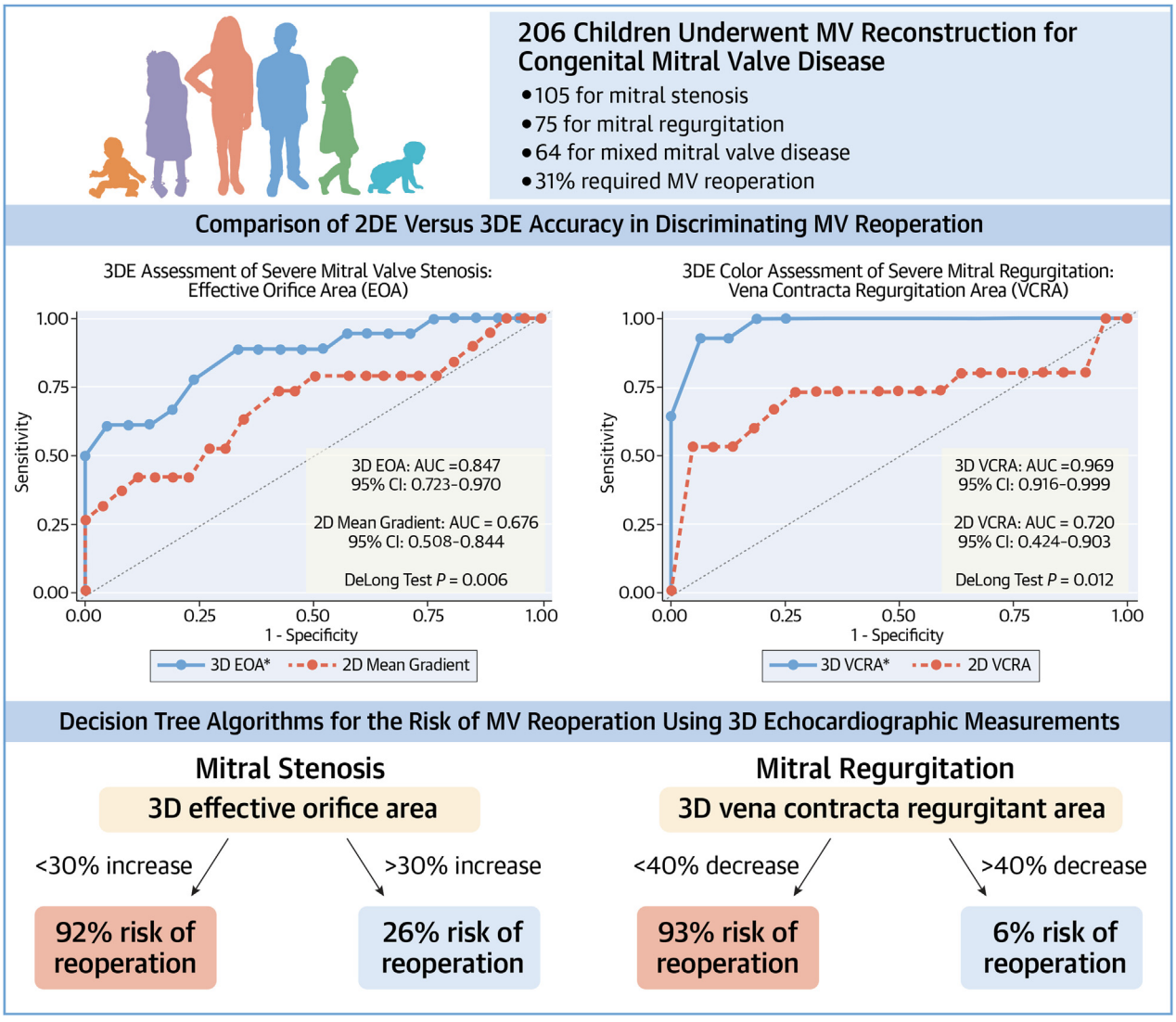
previously reported in literature. 3D imaging allowed assessment of the dynamic motion and 3D spatial construct of all components of the MV including the supra-annular, annulus, chordae, interchordal spacing, and papillary muscles. Such imaging was used to help surgical planning in these patients with complex MV disease.

From an echocardiographic point of view, we found that both 2DE and 3DE parameters were associated with MV reoperation. In particular, evidence of moderate or greater postoperative MR on 2DE, as well as early changes in the 3D-EOA and 3D-VCRA, were all found to be independently associated with the need for MV reoperation.

Postoperative systemic AV valve regurgitation has been shown to be associated with adverse outcomes in a variety of CHDs.[25-28] In 43 adults with CHD undergoing primary or reoperative systemic AV valve surgery, predischarge systemic AV valve regurgitation grade was the only factor associated with adverse outcomes including reoperation.[25] Similarly, studies have shown that postoperative systemic AV valve regurgitation in repaired AV canal is associated with higher risk of AV valve reoperation.[26-28] Given the proven importance of this factor in determining outcomes, studies have also focused on improving 2DE regurgitation assessment with the evaluation of other parameters, such as 2D-VCRA. However, Prakash et al[29] did not find that 2D-VCRA measurements in patients with AV septal defects was superior to the qualitative regurgitation assessment, and Yosefy et al[30] showed that 2D-VCRA can cause clinical misclassification in 45% of adult patients with eccentric MR, while 3D-VCRA was more accurate. In fact, non-negligible changes in the AV valve geometry have been demonstrated in similar populations with CHD after AV valve surgery, as in children with AV canal undergoing AV valve repair.[31] To date, measurements of 2D-VCRA are performed by measuring the VC width mostly in one plane, and in some studies in 2 orthogonal planes. However, these types of measurement do not account for the marked irregularity of shape of the VCRA.

Several publications in adults have highlighted the advantages of 3DE for the quantitative assessment of the valve function,[32-36] with increasing number of reports demonstrating higher accuracy of 3DE compared to 2DE, and higher ability to predict outcome.[37,38] In parallel, a new consensus document recently advised on the use of 3DE for surgical planning in patients with CHD[39] and emphasized that there are only limited data on the impact of 3DE on clinical outcomes in CHD. In the setting of AV valve regurgitation, 3DE directly traces the orifice area without making assumptions on the shape of the VCRA. Simultaneous orthogonal visualization of different planes allows a more precise depiction of the best cross-sectional cutting plane to trace the VC circumference. In adults, a strong correlation has been proven between the 3D-VCRA and the regurgitation area calculated by magnetic resonance imaging.[40] Adubiab et al[38] demonstrated that

CENTRAL ILLUSTRATION **Comparison of 2D vs 3D Echocardiography Accuracy in Discriminating Mitral Valve Reoperation by Area Under the Curve Analysis**



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Left, when considering stenotic valves, AUC curve comparison revealed that early changes in 3D-EOA was more strongly associated with MV reoperation than early changes in 2DE mean gradients (AUC: 0.847 [95% CI: 0.723-0.970] vs 0.676 [95% CI: 0.508-0.844], respectively; DeLong test $P = 0.006$). Right, for regurgitant valves, AUC analysis revealed that early changes in 3D-VCRA was more strongly associated with MV reoperation than 2DE early changes in 2D-VCRA (AUC: 0.969 [95% CI: 0.916-0.999] vs 0.720 [95% CI: 0.424-0.903], DeLong test $P = 0.012$). Decision-tree algorithms: By AUC and decision-tree analysis, an increase in 3D-EOA by <30% leads to 92% risk of MV reoperation whereas an increase >30% is associated with a 26% risk of reoperation (accuracy 80%; HR: 8.5; 95% CI: 2.9-25.1; $P < 0.001$). A decrease of 3D-VCRA <40% is associated with 93% risk of MV reoperation whereas a decrease >40% is associated with a 6% risk of valve reoperation (accuracy 93%; HR: 22.5; 95% CI: 2.9-175; $P = 0.003$). 3D-EOA = 3D effective orifice area; 3D-VCRA = 3D vena contracta regurgitant area; AUC = area under the curve.

measurements of 3D-VCRA were superior to 2DE determination of regurgitation severity. However, experience with quantitative 3DE in children with CHD is still limited, with only a few studies assessing its potential value. Here, we showed that early changes in 3D-VCRA had significantly stronger associations than both, the 2DE qualitative postoperative MR assessment and the early changes of 2D-VCRA.

AV valve stenosis is also known to be associated with adverse outcomes in patients after repair of

TABLE 4 Prognostic Value of 2D and 3D Echocardiography in Assessing the Risk of Mitral Valve Reoperation Based on ROC Analysis and Decision-Tree Algorithms

Mitral Stenosis and Mixed Disease Patients		
Metric	**Change in 2D Mean Gradient**	**Change in 3D-EOA**
AUC (95% CI)	0.676 (0.508-0.844)	0.847 (0.723-0.970)
Best cutoff identified by the decision tree algorithm	<30% increase	<30% increase
Sensitivity	88% (23/26)	61% (11/18)
Specificity	37% (7/19)	95% (20/21)
PPV	66%	92%
NPV	70%	74%
Mitral Regurgitation and Mixed Disease Patients		
	Change in 2D-VCRA	**Change in 3D-VCRA**
AUC (95% CI)	0.720 (0.424-0.903)	0.969 (0.916-0.999)
Best cutoff identified by the decision tree algorithm	<40% decrease	<40% decrease
Sensitivity	47% (7/15)	93% (13/14)
Specificity	95% (21/22)	94% (15/16)
PPV	88%	93%
NPV	72%	94%

AUC curves are plotted and compared in the upper panel of the Central Illustration. Decision-tree algorithms are summarized in the lower panel of the Central Illustration.

3D-EOA = 3D effective orifice area; 3D-VCRA = 3D vena contracta regurgitant area; AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic.

CMVD or AV canal.[10,27,41] MV stenosis is generally assessed by 2DE using mean AV valve inflow gradients; however, this measurement presents several challenges. First, many patients with CHD may have left ventricular systolic or diastolic dysfunction and therefore elevated left ventricular end diastolic pressure, with consequent possible underestimation of the stenosis, if measured using the gradient alone. Additionally, patients may have limited flow across the valve due to the presence of an atrial shunt or low cardiac output. Since gradients are flow dependent, this may also underestimate the magnitude of the stenosis if assessed by mean inflow gradient only. Our study investigated the utility of 3DE assessment in stenotic valves and found that early changes in 3D-EOA were strongly associated with MV reoperation. Most importantly, early changes in 3D-EOA had significantly stronger associations than early changes in 2D mean gradient.

To improve prognostication and facilitate potential application of these findings into clinical practice, decision-tree algorithms were developed and subsequently bootstrapped validated. Potentially, these 3DE parameters could be utilized either preoperatively or in the operating room. The ability to perform these measurements in the operating room would be enhanced with the ability to perform 3D acquisitions in the operating room. Our center has reported the increased diagnostic findings using intraoperative 3DE for aortic valve repairs.[42] Pediatric size 3D transesophageal echocardiography probes are currently in the clinical investigation phase. Early changes in 3D-EOA and 3D-VCRA measured in the operating room may inform decision to return to bypass, or, if these changes are measured at discharge, they may inform earlier follow-up or early MV reoperation.

STUDY LIMITATIONS. Since this is a retrospective study, loss of information occurred and not all patients had 3DE data available. MR severity was graded qualitatively by different echocardiographers and data were extracted from the report; hence, variability in the MR severity assessment may exist. The significant 3DE parameters were calculated using postoperative changes assessed at discharge. We realize the clinical importance of identifying preoperative factors associated with MV reoperation, or using the bypass echocardiogram to help guide patient management. However, in the future, these measurements could be potentially be used in the operating room guiding the decision to return to bypass to correct the anticipated problem of significant regurgitation and/or stenosis. Additionally, this study was limited by constraints of imaging, particular image resolution, and low frame rate. Confidence limits were not adjusted for multiple comparisons and should be interpreted with caution. Finally, the number of events (MV reoperation) in our cohort was relatively limited, thus our preliminary conclusion should be confirmed in larger studies and externally validated. Despite these limitations, we believe this study provides a valuable framework for future research investigations in the field of 3DE and in the assessment of CMVD.

CONCLUSIONS

In a large cohort of patients with CMVD, 31% of patients required MV reoperation at a median follow-up time of 5 years. Age <1 year, presence of tethered leaflets, evidence of moderate or greater postoperative MR on 2DE, as well as early changes in the 3D-EOA and 3D-VCRA were independently associated with MV reoperation. 3DE parameters were found to have a significantly stronger association with MV reoperation compared to 2DE parameters, suggesting added value of the 3DE assessment. Decision-tree algorithms were developed based on these findings to help classify patients and potentially to serve as a support tool for assessment and clinical decision-making.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS 1: Measurements of 3D-EOA and 3D-VCRA can be reliably performed in patients with CMVD and can discriminate outcomes more accurately than measurements of 2DE mean gradients, 2D-VCRA and 2DE MR qualitative assessment.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS 2: Our novel decision-tree algorithms provide clear cutoff points and may serve as a support tool to facilitate clinical decision-making. Changes in 3D-EOA and 3D-VCRA can be measured in the operating room to consider return to bypass, or at discharge, to help inform need for early follow-up and MV reoperation.

TRANSLATIONAL OUTCOME: Future research will further investigate the value of 3DE measurements in discriminating clinical outcomes in CMVD and in other congenital heart valve pathologies, and assess its impact on clinical and surgical decision-making.

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KEY WORDS 3D-echocardiography, congenital mitral valve disease, mitral regurgitation, outcomes, mitral stenosis

APPENDIX For supplemental methods, results, a table, and videos, please see the online version of this paper.