

**Predictors of Transannular Patch Enlargement in Tetralogy of Fallot Repair; a Single Center Experience.**

**ABSTRACTS**

**Introduction:**

Tetralogy of Fallot (ToF) accounts for 5% to 10% of all congenital heart diseases (CHD) and is the commonest cyanotic heart disease beyond the neonatal period. Surgical repair is directed at relieving the right ventricular outflow tract obstruction (RVOTO) and has evolved over time from the frequent use of transannular patch enlargement (TAPE) of the pulmonary valve annulus (PVA), to the more recent trend of conservation of the PVA using valve-sparing surgical techniques. This latter technique is preferred to avoid serious and progressive complications associated with TAPE. The decision on TAPE is primarily based on the PVA z-score which is subject to variability across different surgeons and centers; as such, other parameters have been proposed and some determined to be better predictors of TAPE in ToF surgeries.

**Aim:** To determine the predictors of transannular patch enlargement in ToF surgeries in a CHD specialist center.

**Methods:** This was a retrospective analysis of all patients with ToF who presented at a major CHD center - the Sri Sathya Sai Sanjeevani Hospital (SSSSH), in Raipur India between July 2018 to April 2019. Parameters sought and obtained included patients' demographics, anthropometry and echocardiographic parameters. The z-scores and other derivable variables were calculated and entered into a data base. Analysis using SPSS was done. Descriptive statistics was used to represent continuous variables in means, medians and ranges while categorical variables were represented in bar charts. Analysis of variance was done among group means.

**Results:** There were 135 patients with age range from 7 months to 199 months, with more males 89 (65.9%). TAPE was done in 36(26.7%). The aortic valve diameter (18.3 Vs 20mm,  $p=0.037$ ), Pulmonary valve diameter (10.1 vs 12.0mm,  $P=0.003$ ), and pulmonary valve Z-score (-2.48 vs -1.47,  $p=0.011$ ) were significantly smaller for the group that received TAPE. Univariate analysis of the great artery ratio (PVA/AoV) did not significantly predict TAPE use. However, a GA ratio of  $< 0.54$  was significantly associated with a higher likelihood of having TAPE, odds ratio

2.37(CI: 1.47 to 3.9). Multivariate logistic for use of TAPE in TOF explained 15% (R<sup>2</sup>) of the variance seen in the use of TAPE and correctly predicted 70.8% of the children with TOF who received TAPE. The area under curve for predictability of who received TAPE was 65% (95% CI 53.5% to 76.6).

**Conclusion:** The PVA diameter, Aortic valve diameter and PVA z-score are predictors of TAPE. A GA ratio < 0.54 increases the likelihood of TAPE. Clinical parameters are not useful as determinants of TAPE.

**KEY WORDS: Tetralogy of Fallot Repair, Transannular patch enlargement, predictors.**

## INTRODUCTION

Tetralogy of Fallot (ToF) is the commonest cyanotic congenital heart disease (CHD) and is seen in 5% to 10% of all cases of CHD.<sup>1,2</sup> It is caused primarily by an anomalous antero-cephalad deviation of the developing outlet ventricular septum and an abnormal morphology (hypertrophy) of the septo-parietal trabeculations that encircle the sub-pulmonary outflow tract.<sup>2,3,4</sup> This results in varying degrees of right ventricular outflow tract obstruction (RVOTO) at the level of the infundibulum (45%), pulmonary valve (10%), or combination of both (30%).<sup>1</sup> The deviation underlies all the derivative components of ToF (large misaligned-type VSD, override of the aorta and right ventricular hypertrophy).<sup>3,4</sup> The anatomic anomalies causes a right to left blood shunt at the ventricular level and clinical cyanosis.<sup>1</sup> If left untreated, morbidity from TOF causes a poor quality of life and reduced life span<sup>5</sup>. Tetralogy of Fallot can also co-exist with other cardiac anomalies.<sup>6</sup> Surgical correction is directed at relieving the RVOTO and closure of the VSD, and has evolved over the years with good outcomes.<sup>6-11</sup> Usually, a right ventriculotomy is done to access the RVOTO for resection, then a transannular patch is used to increase the RVOT size.<sup>12</sup> However, this method has a high post-op risk for progressive pulmonary regurgitation (PR) whose medium and long term consequences include right ventricular dilatation and dysfunction, ventricular tachycardia, exercise intolerance with risk of sudden death.<sup>13,14</sup> As such, there has been a shift towards avoidance of a ventriculotomy and the preservation of the pulmonary valve annulus (PVA), while avoiding significant residual RVOTO.<sup>13,15</sup> Surgical techniques currently employed include trans-atrial or trans-atrial/trans-pulmonary approach with better outcomes.<sup>7</sup> However, where the PVA is too small to be preserved, the use of a trans-annular patch for enlargement (TAPE) of the PVA become inevitable.<sup>16,17</sup>

In most centers, the z-score of the pulmonary valve annulus (PVA) is the primary predictor for use of TAPE.<sup>15,18,19</sup> The preoperative echocardiographic PVA z-score has been utilized to guide the surgical decision between a TAPE and valve-sparing surgery<sup>15</sup>. The cut-off value used varies between centers and ranges from 0 to -4.9.<sup>18-20</sup> A study by Choi et al<sup>20</sup> hypothesized and confirmed the use of the great artery ratios (i.e PVA to Aortic valve -AoV) with a cut off value of 0.56, as a better predictor of use of TAPE in their center in Korea.

This study thus aim to explore the determinants of use of TAPE in ToF surgeries, inclusive of clinical and echocardiographic parameters, in our center.

## METHODOLOGY

This was a retrospective analysis of a cross sectional study of all consecutive patients with Tetralogy of Fallot (ToF) presenting over 10 months from July 2018 to April 2019, at the paediatric cardiology clinic of the Sri Sathya Sai Sanjeevani Hospital (SSSSH) in Raipur, India. Institutional ethical clearance was obtained. For the purpose of this study and to ensure uniformity, all patients recruited into the study had their echocardiography performed and measurements taken by the same pediatric cardiologist according to standard protocols.<sup>21</sup> Patients with pulmonary atresia, absent pulmonary valve and atrio-ventricular canal defect were excluded from the study. A normal PVA size was taken from the echocardiographic data of Daubeny and colleagues.<sup>22</sup> The PVA and other parameter z-scores was calculated using the Pedz app by Daniel Grafe.<sup>23</sup> For evaluation of patient factors that could determine route of interventional analysis, only patients by surgeons that have used more than one technique for relief of RVOT obstruction in the previous one year would be analyzed in order to exclude skill or preference bias as a determinant for choice; while patients of those who have used only one type of method would be excluded.

Data were entered into Excel spread sheet and statistical analyses were performed using IBM SPSS Version 23. The outcome of primary interest was to determine the prevalence of use of TAPE in relief of right ventricular outflow tract obstruction in Tetralogy of Fallot in our center and determine Patient-related factors that predispose to the use of TAPE. Descriptive statistics was used to represent continuous variables in means, medians and ranges while categorical variables were represented in bar chats. Analysis of variance was done among group means. Setting cut-off values close to group means, continuous variables were dichotomized and identification of determinants of use of TAPE was done using univariable logistic regression for

all variables. Variables with  $P < 0.1$  and independent variables with clinical relevance to the use of TAPE in ToF repair were put into a model for multivariable logistic regression and a backward stepwise elimination was used to determine the final variables that would be put in the new model. The final model was validated using Hosmer and Lemeshow test goodness of fit test and a ROC curve was done to determine its discriminatory ability.

## RESULTS

A total of 136 children who had tetralogy of Fallot (TOF) were recruited within the study period. One patient was excluded from analysis due to incomplete data. The median age of the study population was 50.5 months (25<sup>th</sup>, 75<sup>th</sup> Percentile: 28,75 months). While age ranged from 7 to 199 months. There were more males 89(65.9%) than females with a M; F ratio of 1.9:1. The median BSA was  $0.6\text{m}^2$  (25th, 75th Percentile: 0.48,  $0.71\text{m}^2$ ). TOF coexisted with other cardiac defects in in 60(44.4%) patients, majority had only one coexisting defect 45(33.3), while the maximum number of coexisting defects was three and this occurred in 4(3.0%) patients. The patients' demographics are summarized in Table 1.

**Table I: Demographics of the study population**

Variable	n or Median (% or IQR)	Range
Age (months)	50.5 (28, 75)	7 - 199
Sex:		
Male	89 (65.9)	
Female	46 (34.1)	
Weight (kg)	12.7 (10, 15)	7 - 58
Height (cm)	98.5 (86, 112)	69 - 165
BMI ( $\text{kg}/\text{m}^2$ )	13.2 (12.4, 14.7)	10.5 - 23.8
BSA ( $\text{M}^2$ )	0.6 (0.48, 0.71)	0.36 - 1.57
AoV diameter (mm)	19 (17, 20.5)	10 - 34.5
AoV Z-score	3.49 (2.6, 4.15)	-0.13 - 5.97
PVA Diameter (mm)	11(9, 12.6)	4 - 19.7
PVA Z-score	-1.8 (-3.19, -0.61)	-7.93 - 1.7
PVA/AoV	0.56 (0.49, 0.66)	0.23 - 1.2
MPA Diameter (mm)	10 (8, 13)	4.6 - 21.7
MPA Z-score	-2.25 (-3.56, -1.02)	-6.96 - 3.77

LPA diameter (mm)	8 (6.8, 9.2)	4.5 - 16
LPA Z-Score	0.06 (-0.78, 0.71)	-3.45 - 3.98
RPA Diameter (mm)	8 (7, 9.5)	4.7 - 17
RPA Z-Score	-0.66 (-1.66, 0.21)	-3.71 - 5.01
Post-Op PV Peak gradient (mmHg)	25.98 (16,33.75)	7- 69

**TOF + other defects:**

No	75 (55.6)
Yes	60 (44.4)

**Frequency of other defects in ToF**

1	45 (33.3)
2	11 (8.1)
3	4 (3.0)

**TAPE:**

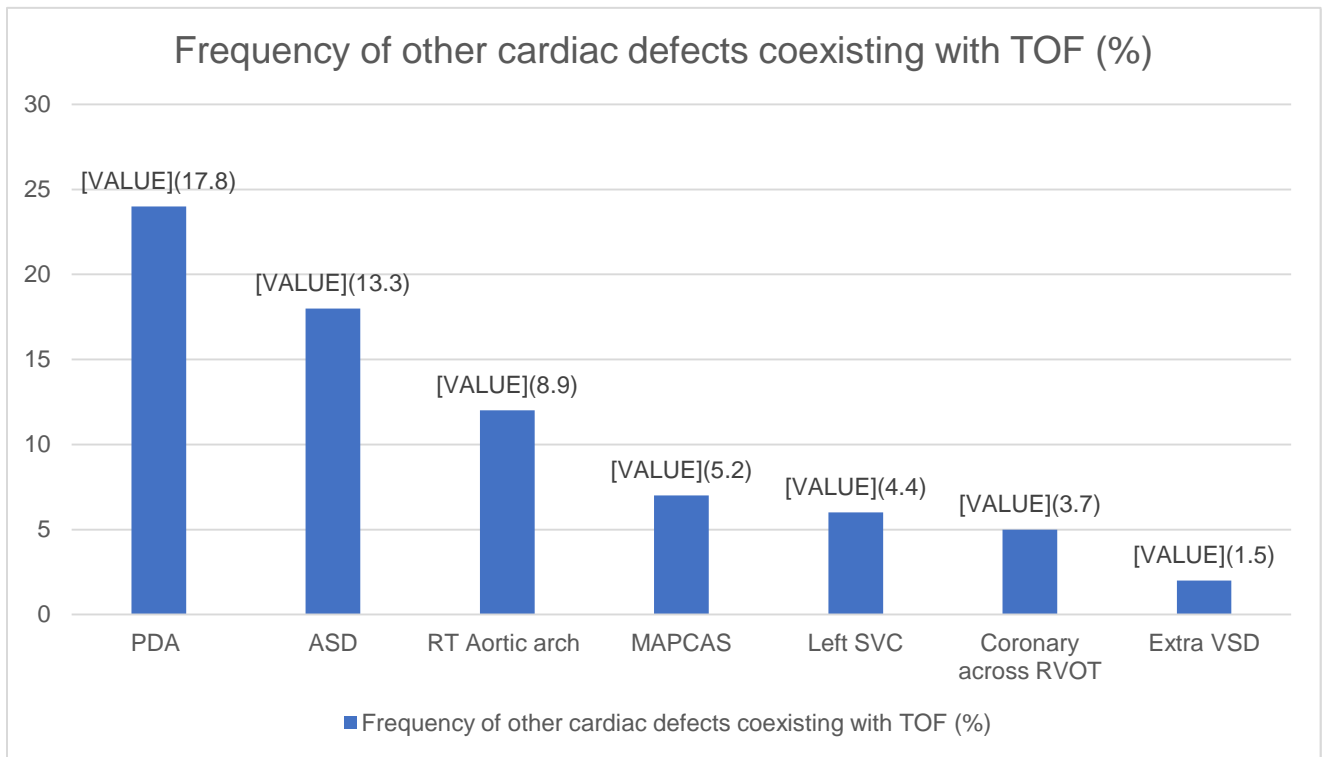
Yes	36 (26.7)
No	99 (73.3)

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IQR: interquartile range, BMI: body mass index, BSA: body surface area, AoV: Aortic valve, PVA: Pulmonary valve annulus, MPA: main pulmonary artery, LPA: left pulmonary artery, RPA: right pulmonary artery, ToF : Tetralogy of Fallot, TAPE: trans-annular patch for enlargement

**Frequency of other cardiac findings co-existing with TOF**

The most common co-existing cardiac finding was patent ductus arteriosus (PDA) in 24(17.8%), followed by atrial septal defects (ASD) 18(13.3%) and right aortic arch 12(8.9%). (Figure 1).



**Fig 1: Frequency of other cardiac findings with Tetralogy of Fallot**

### **Comparison of characteristics of TAPE and Non-TAPE group**

Trans-annular patch enlargement (TAPE) of the pulmonary valve was done in 36(26.7%) patients while relief of RVOT obstruction was done without TAPE in 99(73.3%) patients.

The aortic valve diameter (18.3 Vs 20mm,  $p=0.037$ ), Pulmonary valve diameter (10.1 vs 12.0mm,  $P=0.003$ ), and pulmonary valve Z-score (-2.48 vs -1.47,  $p=0.011$ ) were significantly smaller for the group that received TAPE. Other non-significant parameters that were relatively smaller for the TAPE group include, age, weight, aortic valve Z-score, PVA/AoV ratio and Pulmonary artery measurements as seen in Table II.

**Table II: Comparison of characteristics of TAPE and Non-Tape group.**

Variable	TAPE group Mean ± SD	Non-TAPE group Mean ± SD	P- Value
Age	55.6 ± 36.5	64.4 ± 47.9	0.336
Weight (kg)	13.3 ± 5.3	15.5 ± 9.16	0.191
Height (cm)	99.5 ± 19.1	104.1 ± 24.2	0.333
BMI	13.1 ± 1.32	13.51 ± 2.1	0.286
BSA (M <sup>2</sup> )	0.61 ± .18	0.67 ± 0.26	0.196
AoV Diameter (mm)	18.3 ± 2.31	20.0 ± 4.27	<b>0.037</b>
AoV Z-score	3.24 ± 0.88	3.55 ± 1.23	0.174
PVA Diameter (mm)	10.1 ± 2.56	12.0 ± 3.41	<b>0.003</b>
PVA Z-score	-2.48 ± 1.72	-1.47 ± 1.97	<b>0.011</b>
PVA/AoV	0.55 ± 0.12	0.61 ± 0.61	0.06
MPA Diameter (mm)	10.53 ± 3.73	10.7 ± 3.97	0.812
MPA Z-score	-2.21 ± 2.02	-2.09 ± 1.72	0.769
LPA Diameter (mm)	7.86 ± 1.80	8.51 ± 2.27	0.138
LPA Z-Score	-0.16 ± 1.19	0.16 ± 1.29	0.206
RPA Diameter (mm)	8.28 ± 2.26	8.448 ± 1.87	0.680
RPA Z-Score	-.66 ± 1.61	-0.64 ± 1.24	0.966
Post-Op PV peak gradient (mmHg)	24.9 ± 12.72	25.6 ± 11.16	0.782

BMI: body mass index, BSA: body surface area, AoV: Aortic valve, PVA: pulmonary valve annulus, MPA: main pulmonary artery, LPA: left pulmonary artery, RPA: right pulmonary artery, ToF: Tetralogy of Fallot, TAPE: trans-annular patch for enlargement

### Clinical and Echocardiography features associated with use of TAPE

One hundred and six patients who met the inclusion criteria were analyzed while 28 patients were excluded. For any child with an AoV diameter < 18mm and a PVA diameter < 10mm, the likelihood of having TAPE was increased by odds ratio of 1.8(CI: 1.12 to 02) and 2.3(CI: 1.47 to 3.9) respectively. Also, for any child with PVA z-score below < -2.48 the likelihood of having TAPE was increased by odds ratio 2.17(CI: 1.2 to 3.6). A pulmonary valve to aortic valve ratio (PVA/AoV) of < 0.54 was also significantly associated with a higher likelihood of having TAPE odds ratio 2.37(CI: 1.47 to 3.9). Table III

**Table III: Clinical and echocardiographic features associated with having TAPE**

Variable	TAPE (n= 36) (%)	Odds ratio	95% confidence interval		P- value
			Lower	Upper	
<b>Age</b>					
< 55mths	19 (38.8)	1.3	0.76	2.21	0.44
>55mths	17 (29.8)				
<b>Gender</b>					
Female	12 (40.0)	1.2	0.73	2.19	0.41
Male	24 (31.6)				
<b>Weight of &lt; 12kg</b>					
Yes	14 (38.9)	1.2	0.72	2.11	0.44
No	22 (31.4)				
<b>TOF with other defects</b>					
Yes	22 (37.3)	1.25	0.72	2.16	0.41
No	14 (29.8)				
<b>AoV diameter &lt; 18mm</b>					
Yes	14 (51.9)	1.8	1.12	3.09	<b>0.02</b>
No	22 (27.8)				
<b>AoV Z-score &lt; 3.3</b>					
Yes	17 (42.5)	1.47	0.87	2.49	0.14
No	19 (28.8)				
<b>PVA &lt; 10mm</b>					
Yes	17 (58.6)	2.3	1.47	3.9	<b>0.001</b>
No	19 (24.7)				
<b>PVA Z-score &lt; - 2.48</b>					
Yes	19 (52.8)	2.17	1.2	3.6	<b>0.003</b>
No	17 (24.3)				
<b>PVA/AoV &lt; 0.54</b>					
Yes	17 (58.6)	2.37	1.47	3.9	<b>0.001</b>
No	19 (24.7)				
<b>MPA diameter &lt; 10.5mm</b>					
Yes	22 (42.3)	1.5	0.89	2.65	0.11
No	14 (27.5)				
<b>MPA Z-score</b>					



Yes	16 (34.8)	0.99	0.58	1.68	0.97
No	20 (35.1)				

IQR: interquartile range, BMI: body mass index, BSA: body surface area, AoV: Aortic valve, PVA :pulmonary valve annulus, MPA: main pulmonary artery, LPA: left pulmonary artery, RPA: right pulmonary artery, ToF : Tetralogy of Fallot, TAPE: trans-annular patch for enlargement

### Multivariate logistic analysis for use of TAPE in TOF

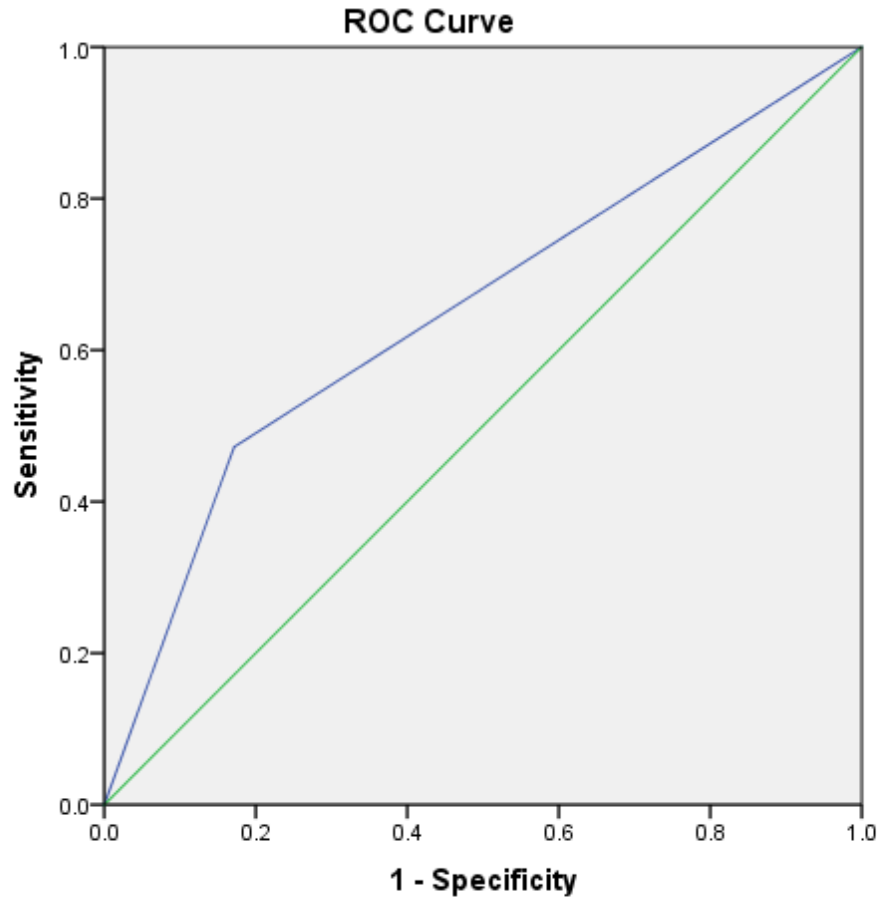
Using clinical relevance, independent variables and a P-value cut off of 0.1 to select the model of best fit, aortic valve diameter (AoV) and pulmonary valve annulus (PVA) diameter were added into multivariable logistic regression model (Table IV). The model explained 15% (R<sup>2</sup>) of the variance seen in the use of TAPE and correctly predicted 70.8% of the children with TOF who received TAPE. The area under curve for predictability of who received TAPE was 65% (95% CI 53.5% to 76.6, these are shown in Table IV and Figure 2.

**Table IV: Multivariate logistic for use of TAPE in TOF**

	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
0 Intercept	1.241	.286	18.825	1	.000			
AoV < 18mm	-.657	.497	1.750	1	.186	.518	.196	1.372
PVA < 10mm	-1.282	.481	7.114	1	.008	.277	.108	.712

Goodness of fit P = 0.727,

Nagelkerke R Square= 0.15



Diagonal segments are produced by ties.

**Fig 2: Multivariate logistic for use of TAPE in TOF**

**Area Under the Curve**

Test Result Variable(s): Predicted Response Category

Area	Std. Error <sup>a</sup>	Asymptotic Sig. <sup>b</sup>	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.650	.059	.011	.535	.766

## DISCUSSION

The study determined that clinical parameters such as younger age, smaller weight, lower height, lower BMI and BSA tended to be lower in ToF patients who needed TAPE compared to those who had valve sparing surgery, but these differences were not significant and as such are not useful as pre-operative predictors of TAPE in ToF surgeries. However, echocardiographic features such as aortic valve diameter, pulmonary valve annulus diameter (PVA) and PVA z-score were significant predictors of TAPE. Literature abound<sup>15,18,19</sup> on the usefulness of the PVA z-score as a determinant of use of TAPE in TOF surgeries, and to date, this has been used to predict the need for TAPE.<sup>18,25</sup> In this study, the PVA z-score was significantly lower in the TAPE group compared to the non-TAPE group. This is similar to findings by Choi et al<sup>20</sup> in Korea. With regards to PVA z-score cut-off values for TAPE, Stewart et al<sup>18</sup> determined that a z-score as small as -4 was still favorable for valve sparing surgery and avoidance of TAPE, whereas Awori et al<sup>19</sup> recommend TAPE use when the z-score is -1.3 or less, and Choi et al<sup>20</sup> got a cut-off value of -1.67. In our study, the cutoff value of the PVA z-score for TAPE was < -2.48. This contrast with findings of Awori et al<sup>19</sup> and Choi et al,<sup>20</sup> but can be deemed to be trending similarly to that by Stewart et al,<sup>18</sup> in that TAPE was used only in the more severe cases of ToF.

The post-operative RVOT peak gradients showed no significant difference between the TAPE and non-TAPE group in the present study, thus strengthening the case for a pre-operative decision for judicious use of TAPE, considering the long-term complication of pulmonary regurgitation. However, there was no comparative analysis of post-operative pulmonary regurgitation between the two groups in this study which presents a limitation for comparison with the other studies<sup>19,20</sup>.

Some author<sup>20</sup> have questioned the reliability of the PVA z-score as a sole determinant for TAPE because it is derived from the absolute value of PVA size which is dependent on the measuring device or imaging technique used, making it prone to inter-user error. Choi et al<sup>20</sup> proposed and confirmed the use of the great arteries (GA) ratio as an independent predictor for use of TAPE, and found a significant difference between the GA ratio in the TAPE and non-TAPE group in their study and that it was a better indicator of TAPE compared to the PVA z-score. This study

got a slightly higher value for GA ratio of 0.55 in TAPE group (compared to 0.51 for the Korean study),<sup>20</sup> but we did not find a significant difference between the GA ratio of the TAPE and non-TAPE groups ( $p=0.06$ ). The reasons for this difference may be age and race related as the median age for the Korean study<sup>20</sup> was much lower than the present study.

Although the GA ratio was not determined to be a significant predictor of use of TAPE in this study, univariate analysis of features associated with TAPE showed that a GA ratio less than 0.54 is significant for use of TAPE. This cut off value can be applied in our center for TAPE, making surgical decision easier. Other significant variables associated with the use of TAPE in the present study are Aortic valve diameter less than 18mm, PVA diameter less than 10mm and PVA z-score less than -2.48. Furthermore, multivariate logistic regression of the AoV and PVA diameters correctly predicted almost three-quarters of patients who would need TAPE thus validating the predictive value of these parameters.

## **CONCLUSION**

The study concludes that the predictors of use of TAPE in ToF repair in our center are PVA diameter < 10mm, aortic valve diameter <18mm, PVA z-score < -2.48 and Great Artery ratio less than 0.54. Clinical profiles of patients are not significant determinants of TAPE use in TOF repair.

## **LIMITATION**

Only echocardiography was deployed as imaging technique in the measures of PVA and other parameters, as such inter-observer errors may affect reproducibility in situations where measurements are taken by multiple echocardiographers.

## **COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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UNDER PEER REVIEW