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Original Article (Pages: 10941-10949)

Investigating Diverse Structure of Pulmonary Blood Vessels in Patients with Combined Pulmonary Atresia and Ventricular Septal Defect and Examining the Effect on Surgery Result

Reza Shakeri[1], *Abdolrahim Ghasemi[2], Ramin Baghaei Tehrani[3]

[1]Pediatric Cardiology Fellowship, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [2]Associate Professor of Pediatric Cardiology, School of Medicine, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [3]Associate Professor of Cardiac Surgery, School of Medicine, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background

This study aimed to investigate diverse structure of pulmonary blood vessels in patients with combined pulmonary atresia and ventricular septal defect and examine the effect on surgery result.

Materials and Methods

This cohort retrospective study was conducted on admittances to Tehran and Sari Hospitals at 2005-2016 for pulmonary atresia with ventricular septal defect (PA-VSD) with pulmonary artery (PA) anatomical variation. Diagnosis of pulmonary blood vessels in patients with PA-VSD was based on the results of CT Angiography (CTA), MRI, or cardioangiography examinations. Patients were followed up clinically by means of imaging in the course of initial repair, pre-definitive surgery preparation, and post-operative stages. All data sets were analyzed using Stata software version 13.0.

Results

Abundancy of PA-VSD classes A, B, and C was 34 (37.8%), 51 (56.7%), and 5 (5.6%) individuals respectively, while mean age and standard deviation of subjects for each of the said groups was 166.5±75.6, 135.79±5.3, and 108.4±152 months respectively. 38 (42.2%) were 1-year or younger at the time of initial surgery. As regards between-class age distribution, 18 (52.9%) individuals in group A, 20 (39.2%) individuals in group B, and the entire 5 individuals in group C were collectively above the age of 1 years old.

Conclusion

In view of the recent studies and the present investigation involving 90 patients with PA-VSD, it is easy to apprehend the large-scale applicability of complete-repair surgical interventions for patients suffering from this disease. This holds true specifically for class A patients who enjoy a longer lifespan and a more favorable prognosis.

Key Words: Children, Pulmonary Atresia, Pulmonary Blood Vessels, Ventricular Septal Defect.

*Please cite this article as Shakeri R, Ghasemi A, Baghaei Tehrani R. Investigating Diverse Structure of Pulmonary Blood Vessels in Patients with Combined Pulmonary Atresia and Ventricular Septal Defect and Examining the Effect on Surgery Result. Int J Pediatr 2020; 8(2): 10941-949. DOI: **10.22038/ijp.2020.45965.3747**

Corresponding Author:

Abdolrahim Ghasemi, Assistant Professor of Pediatric Cardiology, School of Medicine, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Email: rbaghaei@sbmu.ac.i

Received date: Aug.15, 2019; Accepted date: Jan.12, 2020

1- INTRODUCTION

Pulmonary atresia with ventricular septal defect (PA-VSD) combined with pulmonary artery (PA), remaining small or main pulmonary artery (MPA) not being formed at all, is a birth defect that carries a high rate of morbidity and mortality while serving as a challenge for physicians dealing with congenital conditions. Despite the remarkable progress made in the field of surgical interventions and transcatheter (TC) practices, controversy remains in selecting the optimum treatment approach for this group of patients. Based on Barbero-Marcial classification, the defect can be divided into the following three classes (1):

Class A: Presence of connected Pas but blood abnormally transmitted via a persistent opening between the two major blood vessels; a condition known as "patent ductus arteriosus" (PDA);

Class B: Pas not fully developed and part of the segments being supplied from descending aorta through separate major aortopulmonary collateral arteries (MAPCAs);

Class C: Total absence of MPA and entire lung arteries being fed from descending aorta by means of MAPCAs.

Infants with PA-VSD and MAPCAs running between aorta and main pulmonary artery require surgery in order to survive. However, the choice of best surgical approach varies controversially, depending on the anatomy of PAs and the age and weight of the patient. For many decades, deciding on the ideal surgical management has been a matter of dispute. In broad outline, there are two principal surgical approaches:

i- Unifocalization (integrated approach) involving anastomosis of collateral arteries to a central conduit in order to create a main pulmonary artery (2, 3);

ii- Strategy of rehabilitation whereby a surgical shunt is initially created to allow the growth of central pulmonary arteries in the early stages of life (4), and once these arteries have sufficiently developed, delivering surgical repair (5).

Meantime, the third group of experts is in favor of applying the above measures in a combined form. Despite the tremendous advance made in surgical interventions and transcatheter practice, deciding on the optimum treatment approach for this group of patients remains controversial. Hence, this study aimed to investigate diverse structure of pulmonary blood vessels in patients with combined pulmonary atresia and ventricular septal defect and examine the effect on surgery result.

2- MATERIALS AND METHODS

This cohort retrospective study was conducted on admittances to Modares, Atieh, Lavasani in Tehran and Imam Khomeini in Sari Hospitals in the 2005-2016 period for PA-VSD with PA anatomical variation. Study population was selected using census methods. Exclusion criteria included defective medical record and/or lack of valid imaging (e.g. CT Angiography (CTA), magnetic resonance imaging (MRI), or cardioangiography). At first, demographic data including age and BMI were collected. Diagnosis of Pulmonary blood vessels in patients with PA-VSD was based on the results of CTA, MRI, or cardioangiography examinations.

Submitted patients suspected of PA-VSD were initially examined by aforementioned imaging tests before being categorized into 3 groups according to their pulmonary circulation structure (i.e. Barbero-Marcial classification). Treatment was applied in the form of initial repair or definitive treatment. Patients were followed up clinically by means of imaging in the course of an initial repair, pre-definitive

surgery preparation, and post-operative stages. Necessary pulmonary structure correction was made using catheterization or different surgical procedures. Surgical results, effectiveness, adverse effects, and patient death (during treatment and follow-up stage) were comparatively analyzed relative to the natural course of patients in different groups. Appropriate patient follow-up was carried out based on medical records or upon patient summoning and those lacking required information were excluded from the study.

In compliance with ethics and confidentiality principle, patient information, including demographic and experimental data, remained undisclosed. Meanwhile, mean and standard deviation was used to interpret qualitative data, while grouped data were interpreted in terms of abundance and percentage.

Furthermore, use was made of Chi-squared (X^2), and Fisher's exact tests for measuring between-class independence. Comparison of survival rates between different groups was also made by a variety of methods such as Kaplan-Meier estimator and log-rank test and COX model was employed to evaluate the effect of variables on the duration of surgery for each group. All data sets were analyzed using Stata®-v13 software. A P-value of 0.005 and less (P-value≤0.005) was determined to signify minimum statistically significant difference.

3-RESULTS

Data gathered from 90 children from the age of 6 days to 397 months with congenital cardiac disorders was collectively considered in this study. Abundancy of PA-VSD classes A, B, and C was 34 (37.8%), 51 (56.7%), and 5 (5.6%) individuals respectively, while mean age and standard deviation of subjects for each of the said groups was 166.5±75.6, 135.79±5.3, and 108.4±152 months, respectively. Small sample size in the case of PA-VSD class C justified the large deviation obtained for this group and, henceforth, only groups A and B were incorporated in the main analysis. Moreover, the abundance of Trans-catheter (TC), and mean age of referrals at the time of TC was also examined. Abundance of TC was reported 28 (82.4%), 27 (52.9%), and 2 (4%) for groups A, B, and C, respectively. In the meantime, individuals with class B possessed the highest mean age of referrals at the time of TC. One-way analysis of variance (one-way ANOVA) showed no significant difference existing between the triple groups as to TC age (P-value=0.15). COX model was employed to evaluate the effect of age on the duration of surgery for groups A and B. Findings suggest no association between patient age and death following initial surgery.

Nor did it discover the during-surgery age to be associated with deaths in either of the two A and B groups. TC-age analysis also showed an approx. 0.3% increase in the risk of death per month of age, which is not statistically significant (P-value=0.71). On the other hand, in group B, the risk of death was found to reduce by approx. 0.7% per month of age, which again was not considered statistically meaningful (P-value=0.50). According to obtained data, 6 (17.6%) out of a total of 34 individuals in group A, 24 (47.1%) out of a total of 51 individuals in group B, and 3 out of a total of 5 individuals in group C did not receive TC (**Table.1**).

Of the overall 90 participants in the present investigation, 38 (42.2%) were 1-year or younger at the time of initial surgery. As to between-class age distribution, 18 (52.9%) individuals in group A, 20 (39.2%) individuals in group B, and the entire 5 individuals in group C were collectively above the age of 1 (**Figure.1**).

Table-1: Comparison of mean TC age according to defect class, as well as the effect of initial surgery age on subject death.

Congenital Defect Type	Mean	SD	P-value	Risk	P-value
Class A	71.2	68.5	0.15	0.1-995.022	0.22
Class B	47.6	63.3		1.009	0.31
Class C	26.4	36.3		0.1-9450.18	

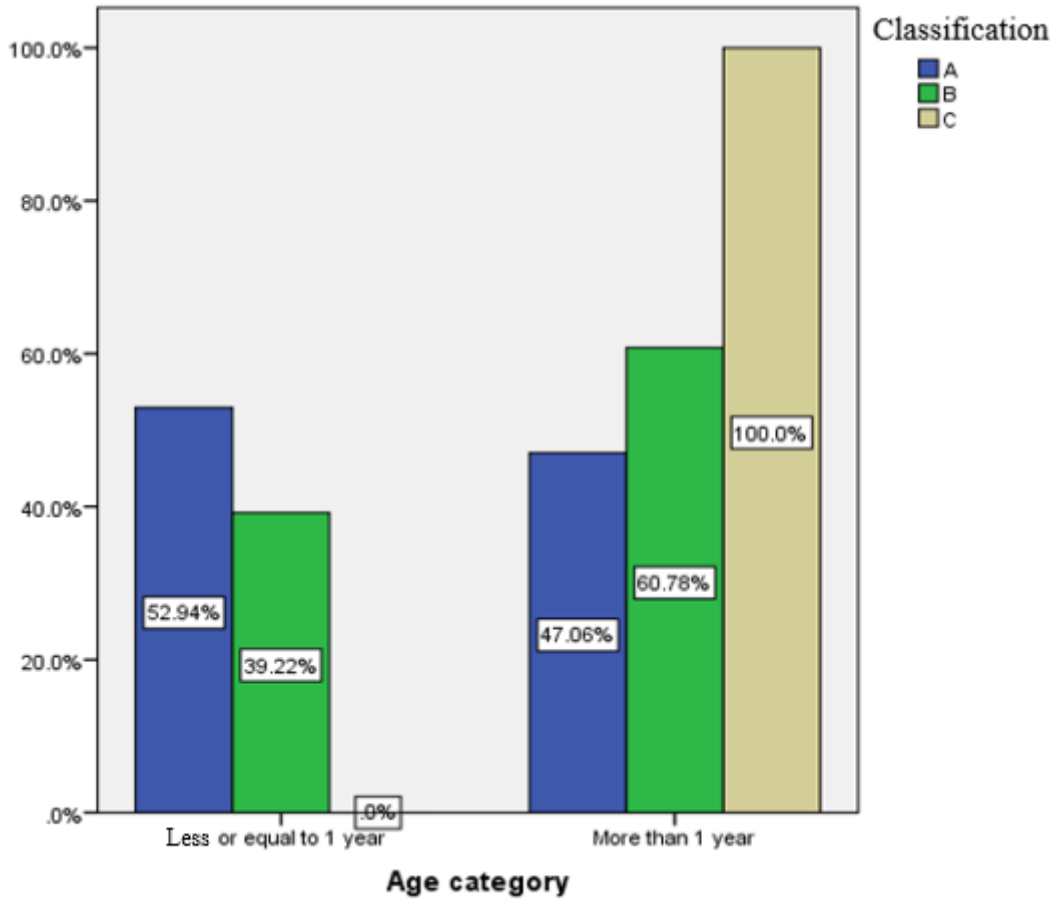

Fig.1: Percentage of patients with 1-year of age and younger according to defect class.

Total intervention required per group for patients subject to current investigation is presented in **Table.2**. As the table illustrates, requirement for intervention prior to TC surgery is highest for class B individuals as compared to other classes. Additionally, minimum age at the time of initial surgery for all groups was on birth and 15 days after birth respectively. Also, figures on the number of post-TC interventions for class A indicates 19 cases of non-intervention, 9 cases of single intervention, 3 cases of double intervention, a single case with 3 interventions, and another single case with 5 interventions.

Table-2: Abundance of pre-TC and Post-TC requirement for re-intervention among studied individuals.

Stage	No. of Re-interventions	Class A No. (%)	Class B No. (%)	Class C No. (%)
Pre-TC Surgery	Not required	22 (64.7)	8 (15.7)	-
	Once	5 (14.7)	14 (27.5)	3 (60)
	Twice	7 (20.6)	14 (27.5)	-
	Three times	-	10 (19.6)	1 (20)
	Four times	-	2 (3.9)	1 (20)
	Five times	-	3 (59)	-
Post-TC Surgery	Not required	19 (55.9)	42 (82.4)	4 (80)
	Once	9 (26.5)	5 (9.8)	-
	Twice	3 (8.8)	3 (5.9)	1 (20)
	Three times	1 (2.9)	1 (2)	-
	Four times	-	-	-
	Five times	1 (2.9)	-	-

The mean and minimum weight of patients at the time of initial surgery was 13.45±10.7 kg and 3 kg, respectively. Alternately, the mean and minimum weight of patients at the time of TC was 13 ±13.2 kg and 5 kg, respectively, with the youngest TC-receiving subjects being 5 months old. With respect to the relationship between total number of interventions and survival rate for class B, results show no significant relation (P-value=0.87). Similarly, independent t-test results indicate no significant difference existing between the two intervention-requiring and no intervention-requiring groups in terms of patient lifespan (P-value >0.05). Meanwhile, the effect of higher/lower than age 1 at the time of TC on patient survival rate could not be established owing to the small number of samples below the age of 1 at the time of TC (3 patients). The **Table.3** illustrates a difference in the between-class mean body-mass index at the time of TC (P-value=0.023). However, this difference was not observed at the time of initial surgery. Findings also show the mean number and standard deviation of MAPCs for each of the triple classes to vary from 0.09±0.28 in class A to 3±1.11 in class B, and 1.6±2.4 in class C. The highest MAPC count of 5 was recorded for class A and B defects. At the same time, Kaplan-Meier estimator demonstrated no significant difference in survival rate for 1-year and less as compared to over 1-year age groups at the time of initial injury.

Table-3: Mean body-mass index of individuals at the time of TC and initial surgery compared.

Time	Congenital Defect Type	Mean Body-Mass Index	Standard deviation	P-value
At time of initial surgery	Class A	1.77	0.5	0.46
	Class B	0.55	0.29	
	Class C	0.75	0.42	
At time of TC	Class A	0.65	0.41	0.023
	Class B	0.4	0.44	
	Class C	0.27	0.36	

For all 3 classes of the present study, comparison was made between patient lifespan after initial surgery, patient lifespan post-TC, patient lifespan in the 1-year and less age group and over 1-year age group, as well as patient-lifespan in intervention-requiring and no intervention-requiring groups. According to the results, no between-class significant statistical difference exists in terms of lifespan at the initial-surgery stage (P-value=0.36), as opposed to that at TC stage where a significant difference is denoted (P-value=0.019). For the next stage, only classes A and B were compared owing to class C small sample size. Data presented in Table 6 for this stage is the outcome of

the difference in survival rate of groups A and B with the somewhat lower rate recorded for group C. Moreover, lifespan of patients in the 1-year and less age group at the time of initial surgery does not significantly differ from those above the age of 1 (P-value=0.24). Meanwhile, the one-way analysis of variance for age (lifespan) of subjects in the triple defect classes shows no statistically significant difference. It applies to the lifespan of intervention requiring and no intervention-requiring groups comparison (P-value=0.34). Patient lifespan subsequent to initial surgery (a), estimation of post-TC survival-rate (b), lifespan of patients in 1-year and less age group and over 1-year of age compared (c), and survival rate of patients in intervention-requiring as compared to no intervention-requiring groups (d) are presented in **Figure.2**

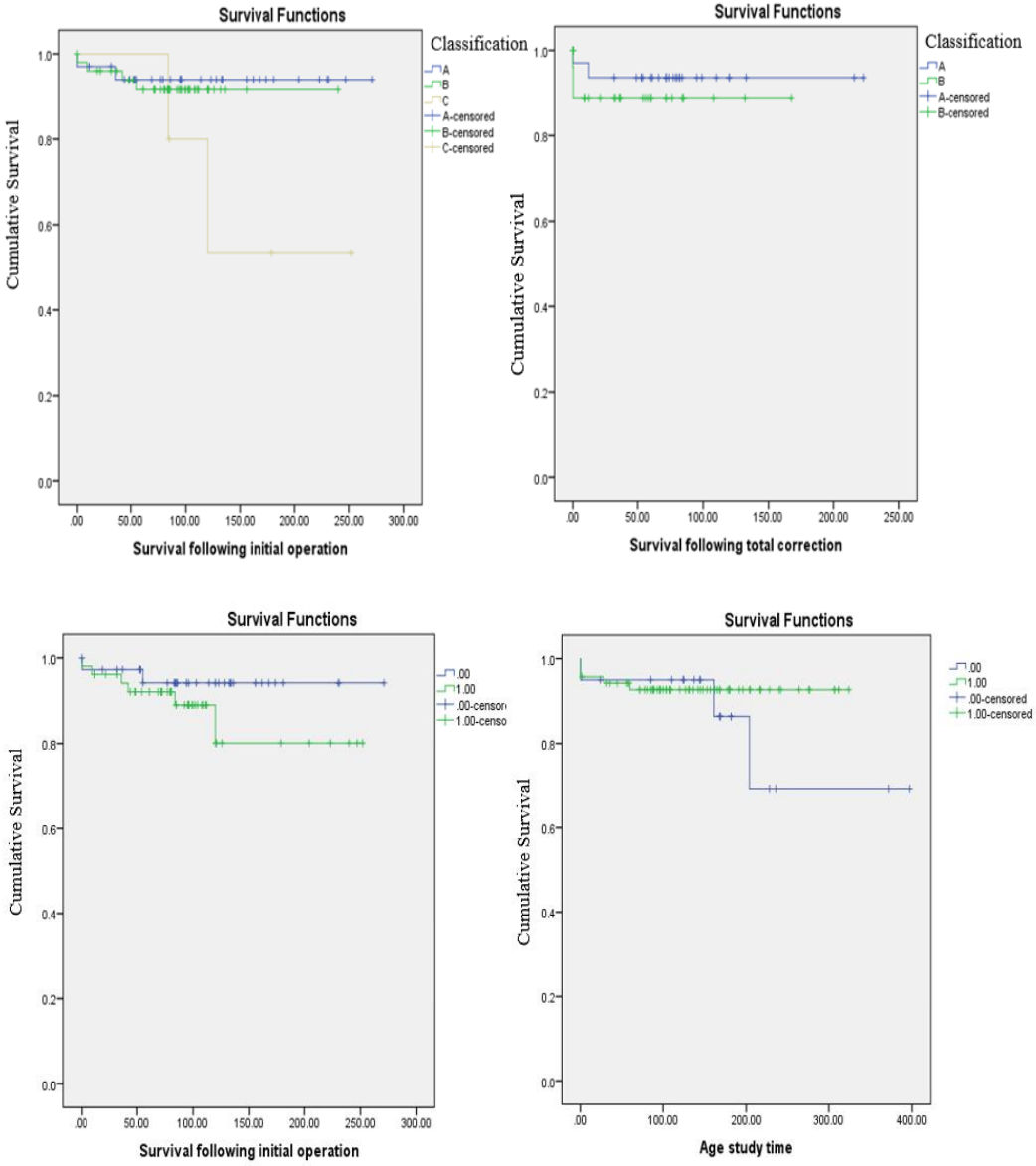

Fig.2: Patient lifespan subsequent to initial surgery (a), estimation of post-TC survival-rate (b), lifespan of patients in 1-year and less age group and over 1-year of age compared (c), and survival rate of patients in intervention-requiring as compared to no intervention-requiring groups (d).

4- DISCUSSION

This study aimed to investigating Diverse structure of pulmonary blood vessels in patients with combined pulmonary atresia and ventricular septal defect and examining the effect on surgery result. Abundancy of PA-VSD classes A, B, and C was 34 (37.8%), 51 (56.7%), and 5 (5.6%) individuals respectively, while mean age and standard deviation of subjects for each of the said groups was 166.5±75.6, 135.79±5.3, and 108.4±152 months respectively. 38 (42.2%) were 1-year or younger at the time of initial surgery. As to between-class age distribution, 18 (52.9%) individuals in group A, 20 (39.2%) individuals in group B, and all 5 individuals in group C were collectively above the age of 1.

Estimated survival rate of these patients in the absence of surgical intervention is 50% until the age of 1 and 80% until the age of 10. Number of patients having reached adulthood without receiving surgical treatment is tremendously low. Some articles reported the average age of survival did not exceed the 3rd life-decade in the absence of surgical intervention, with the eldest individual in their investigation being reportedly 54 years old (6-8). Mean age of patients receiving complete TC repair surgery was 6 years in group A and 4 years in group B.

In other words, patients with class B defect had requested surgery at an earlier age. This could be because of surgeons' reluctance to apply surgery until later years owing to more improved PA anatomy and, consequently, better clinical conditions exhibited by class A patients. Nonetheless, no statistically significant difference was found between the two groups with respect to the age of receiving complete TC surgery. In the meantime, findings suggest the death risk rate increases by 0.3%. However, this is of no significance statistically. For group B, a decrease of 0.6% per month of age is suggested which is also of no statistical difference. The latter result could, perhaps, be justified by the fact that class B patients require reconstruction of left and right pulmonary arteries (PAs), and concurrent closing of a series of MPCAs which, technically speaking, is more conveniently practiced and less prone to adverse effects with increasing age (9). In comparing the triple groups in terms of patient lifespan after initial surgery, no statistically significant difference is observed. As the results suggest, group A with approximately 19 years has the longest chance of survival, followed by group B with approximately 18 and group C with approximately 15 years, respectively; a justifiable result with respect to the intensity of disease and complications facing patients.

As opposed to the significant difference observed for patient lifespan between class A (17.5 years), and class B defects subsequent to complete repair surgery, signifying improved prognosis following this intervention in group A cases as compared to group B. Class was excluded from this comparison due to smallness of sample size (10). Of the total 90 participants in the present investigation, 38 (42.2%) were 1 year or younger at the time of initial surgery. As opposed to 18 (52.9%) in group A, 20 (39.2%) in group B, and all 5 individuals in group C who were above the age of 1. Better general condition of class A patients in terms of PA anatomy and branches has most likely delayed the need for early surgery; while in class B patients suffering from poor circulation and more critical PA anatomy on left and right, implementing earlier surgery (below the age of 1) by means of shunting was determined crucial. With regard to class C patients, abundance of MPACAs not only improved circulation but also generated overflow, diminishing the requirement for surgery until later stage (over the age of 1). Nevertheless, small size of sample in group C prevents

us from making firm judgments until similar inquiry is made with a larger sample (10-14). Additionally, in group B patients, no significant relationship was discovered between number of interventions and patient survival rate. In the same way, there was no significant difference between group requiring intervention and group not requiring intervention in terms of patient lifespan. This allows us to deduce that cases requiring transcatheter were generally in a more critical condition and had a shorter life expectancy. However, after receiving different transcatheter interventions, both the general condition and survival rate improved, particularly for class B patients.

Based on the obtained results, mean lifespan of patients in the triple groups was determined to be 13.8 years for group A, 11.2 years for group B, and 9 years for group C. Meantime, one-way analysis of variance does not show a meaningful statistical difference between the ages of individuals. Mean survival time of patients receiving and not receiving transcatheter was 25 and 27 years, respectively, which again reflects no statistically significant difference (P=0.34).

However, transcatheter can be concluded to have relatively closed the gap between the lifespan of patients with more severe clinical and anatomical conditions and those with less severe clinical and anatomical conditions; an observation clearly underscoring the importance of transcatheter as an efficacious treatment intervention. Meanwhile, independent t-test results also failed to show any meaningful statistical difference in the age of individuals between groups receiving and not receiving TC. This implies TC is not significantly related to individual's age and that considering scientific indications of intervening should suffice (11-13). Relatively larger sample size, focusing on the results of surgical operations and contemplating patient's need for various catheter interventions can be collectively recognized as the advantages of the present research over the analogous studies. In the course of this investigation, mean age of individuals with PA-VSD never receiving surgical intervention was not taken into account, leaving us bare-handed in terms of data concerning natural course of patients. We, therefore, had to compare our own results with the natural course of patients involved in other studies, a process that can be deemed as a major limitation to this research.

5- CONCLUSION

In view of the recent studies and the present investigation involving 90 patients with PA-VSD, it is easy to apprehend the large-scale applicability of complete-repair surgical interventions for patients suffering from this disease. This holds specifically true for class A patients who enjoy a longer lifespan and a more favorable prognosis. On the other hand, when speaking of survival time and lifespan, catheter-based interventions can prove equally beneficial for individuals with critical clinical and anatomic conditions by helping them close in on those with less severe clinical and anatomical conditions.

6- CONFLICT OF INTEREST: None.

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