MAGNITUDE OF RESIDUAL SHUNT AND ASSOCIATED FACTORS AMONG CHILDREN SURGICALLY TREATED FOR PATENT DUCTUS ARTERIOSUS AT TIKUR ANBESSA SPECIALIZED HOSPITAL AND CARDIAC CENTER, ADDIS ABABA, ETHIOPIA

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A research proposal to be submitted to the Department of Surgery in partial fulfillment of the requirement for a Subspecialty Certificate in Cardiothoracic Surgery

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August 2024

Addis Ababa, Ethiopia

DECLARATION

I, Abdela Hayato, hereby declare that this research proposal is a result of the works of my own making, except where credit is given in a review of the previous literature in the content and by my knowledge, has never been submitted for any academic award or qualifications in this institution.

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ABBREVIATIONS/ACRONYMS

AAU: Addis Ababa University

ASD: Atrial Septal Defect

CCE: Cardiac Center of Ethiopia

CHD: Congenital Heart Disease

CHS: college of health sciences

CICU: Cardiac Intensive Care Unit

CT: Computed tomography

CXR: Chest X-Ray

ECG: Electrocardiogram

HDsPDA: Hemodynamically significant PDA

ICU: Intensive Care Unit

OR: operation Room

PAH: Pulmonary Artery Hypertension

PDA: Patent Ductus Arteriosus

PTDC: Percutaneous transcatheter device closure

TASH: Tikur Anbessa Specialized hospital

USA: United States of America

VSD: Ventricular Septal Defect

WHO: World Health Organization

ABSTRACT

Background: Patent ductus arteriosus is a congenital heart disease where the fetal ductus arteriosus does not close spontaneously after birth. Unless treated, its persistence results in non-physiologic blood flow between the proximal descending thoracic aorta and the pulmonary artery. Among the operated patients with double ligation, 2 to 23% of them may develop residual shunts which may complicate with rare but fatal endarteritis and embolic phenomena. However, little is known about the magnitude of residual shunt and associated factors among children operated for patent ductus arteriosus in Ethiopia.

Objective: To assess the magnitude of residual shunt and associated factors among children operated for patent ductus arteriosus at Tikur Anbessa Specialized Hospital and Cardiac Center, Addis Ababa, Ethiopia.

Methods: A hospital-based cross-sectional study was conducted by a retrospective chart review of 167 eligible children operated on from January 1, 2021 to December 31, 2023. The collected data was coded, cleaned, and exported into SPSS version 25 for analysis. Categorical variables were summarized using frequency tables and figures. Descriptive variables were summarized by using measures of central tendency and dispersions. Binary logistic regression analysis was conducted to check the associations between independent and outcome variables. Multivariate logistic regression analysis was employed to identify factors statistically associated with residual shunt. The strength of association was determined by using an adjusted Odds Ratio with its 95% confidence interval. Statistical significance was declared at a P-value <0.05.

Result: The median (± interquartile range) age of the participants was 4.2(± 5.0) years. Among the study participants, 112(67 %) were females. The magnitude of residual shunt among children operated for patent ductus arteriosus was 22.2% (95% CI= 16.2 -28.1)**.** In multivariate logistic regression analysis, only the presence of pulmonary hypertension showed a statistically significant association with residual shunt among children operated for PDA with surgical ligation. Accordingly, children who had pulmonary hypertension were 2.80 times (AOR=2.80, 95% CI: 1.265, 6.222) more likely to develop residual shunt after ligation for PDA compared to children who had no pulmonary hypertension before surgical intervention.

Conclusion and Recommendation: The immediate post-operative prevalence of residual shunt in those patients for whom PDA ligation was done was significantly high in our setup. Another surgical approach, which is division and closure, should better be considered instead to avoid the risk of residual shunt and its long-term complications, particularly for children with pulmonary hypertension.

Keywords: Patent ductus arteriosus, Surgical treatment, Residual shunt, children, Ethiopia

1. INTRODUCTION

1.1.Background

Globally congenital heart diseases (CHD) are the most common birth anomalies. The majority of those children with congenital heart diseases survive to adulthood due to better cardiological and cardiac critical care in high-income countries(1).

Patent ductus arteriosus (PDA)is estimated to account for around 10% of all congenital heart diseases, the incidence of which is around 2-4 per 1000 term births(2–4). It is one of the frequently occurring congenital heart diseases where the fetal ductus arteriosus does not close spontaneously after birth. Its persistence results in non-physiologic blood flow between the proximal descending thoracic aorta and the pulmonary artery (5). Its persistence is important for fetal survival because the lung is not functional and it is fluid-filled in utero. More than 65% of cardiac output depends on the Right ventricle and without PDA or other shunt lesions, the right ventricle faces extreme afterload which leads to worse outcomes (6).

Preterm infants have a higher incidence of PDA due to altered physiologic mechanisms involved in PDA closure such as increased oxygen tension, and increased elimination of levels of circulating prostaglandins(7). After birth, there is a change to intravascular condition rapidly as the fluid-filled lungs start to be functional getting more blood flow accompanied by the placental exclusion from the circulation. This increase in oxygen tension and decreased placental origin prostaglandins causes contraction of the ductus vascular smooth muscle resulting in early functional closure by contraction of the ductus vascular smooth muscle. This usually takes place within the first 24-48 hours of birth. Finally, the closed ductus will remain as a fibrous cord with no lumen (ligamentum arteriosus). If it persists beyond one week, it is less likely that it is closed spontaneously(6).

Even though ductus arteriosus serves to maintain circulation in utero, its patency after birth has various health consequences. If it is not closed early with possible effective approaches, there will be pulmonary over-circulation which leads to pulmonary hypertension causing irreversible pulmonary vascular disease, congestive heart failure, and finally death(8).

Most infants with PDA are asymptomatic, particularly those with small ‘silent’ PDA. In the remaining the presentation can be cough, shortness of breath, failure to thrive, and repeated hospital visits for recurrent respiratory tract infections to full-blown congestive heart failure in

moderate to large PDA. There is a typical continuous machinery murmur at the upper left sternal border or in the left infraclavicular area on auscultation. This murmur may be absent in those with markedly elevated pulmonary vascular resistance due to pulmonary overcirculation (3,6). The magnitude of shunting across the PDA determines the hemodynamic impact in a patient with an otherwise normal cardiovascular system. If the pulmonary vascular resistance is not significantly elevated, shunting across the duct is exclusively left-to-right as the lungs expand with initiation of spontaneous breathing soon after birth. In patients with untreated, large, nonrestrictive, or minimally restrictive PDAs, irreversible pulmonary vascular disease with reversal of shunt from right to left may occur gradually over time due to longstanding pressure and volume overload in the pulmonary circulation. This condition, which contraindicates surgical intervention, is commonly referred to as Eisenmenger syndrome. Therefore, closure of large PDAs is recommended during the early years of life, preferably within the first 6 months of life for better outcomes (6).

Those children having clinical suspicion of PDA will be confirmed by Transthoracic Echocardiography which will give us information about the size of PDA, direction of shunt, and associated other congenital cardiac lesions(7,9).

Management of PDA includes medical (using intravenous indomethacin, Ibuprofen, acetaminophen) early after birth, Percutaneous transcatheter device closure (PTDC), and Surgical management which includes ligation or complete division(9,10).

Surgical management can be PDA ligation or division and closure. However, it is controversial as to which option is the most effective way of management so far. The magnitude of residual shunt in those children for whom PDA ligation done so far is not known in our setup.

1.2. Statement of the Problem

Patent Ductus Arteriosus (PDA) is a commonly encountered congenital cardiovascular birth anomaly and if it happens, it is associated with short-term and long-term adverse health outcomes(7).

The global prevalence of unrepaired congenital heart disease in school-aged children was 3.809 (3.075, 4.621)/1000 children which varies in different geographical regions of the world. Africa had the highest prevalence of unrepaired CHD in school-aged children out of which PDA accounted for 13.9% and was reported as the third commonest overall prevalence of unrepaired CHD following VSD(30.3%) and ASD(24.5%)(1).

The burden of congenital heart disease including PDA is also high in Ethiopia as comprehensive cardiac care is yet inadequate like other African countries. In a study done in four public Hospitals in Addis Ababa, the prevalence of overall CHD was 35.8% and the prevalence of PDA was 15.5% among children who presented to these hospitals with confirmed diagnosis of congenital anomalies (11). Of those patients with congenital heart disease who were operated at the cardiac center of Ethiopia, Patent ductus arteriosus (PDA) accounted for 33.3% followed by VSD with 29.5% (12).

Residual patency of doubly ligated duct may occur because of either recanalization or incomplete occlusion during surgical closure(13,14) and the rate of residual ductal flow was around 2% to 23% in another study (7,15). Sometimes transfixion is added to double Ductal ligation to decrease the risk of residual flow. However, even such intervention did not completely avoid the risk to nil unlike that of division and closure which completely avoids the risk of residual shunt. Long-term follow-up is required as there is a possibility of residual shunt even months or years after surgical intervention(4,13).

There are considerable complications after PDA surgical interventions such as infective endarteritis which remains a significant health issue in countries with limited health resources and access to health care. Pulmonary embolism which can also occur in patients with even small PDAs including those with residual shunts after surgical intervention are additional grave complications encountered after PDA ligation(6,16,17).

The main goals of PDA closure are to have complete occlusion of the left-to-right shunt and to prevent the risk of bacterial endocarditis. Detected residual shunt or patency should be considered as a failure of the surgical procedure. The presence of residual shunt can also be traumatic for those parents who are informed that their child has a residual PDA after surgical ligation(18).

Transcatheter closure of residual postsurgical arterial duct is a safe and successful procedure, but the distorted shape of the arterial duct after surgical ligation makes it challenging for percutaneous intervention(4,18). This further makes the condition worse in our setup because we don’t have routine percutaneous interventions even for those who have intact, non-manipulated ductal anatomy, let alone post-operative patients with residual patency.

Medical management of PDA has not yet started as routine care and percutaneous devise closure is also mainly mission-based. So, surgery remains the main routine management option in our setup. Even though division and closure are the standards of care in the management of PDA, ligation remains one of the most commonly practiced surgical procedures worldwide including in our country. However, shreds of research literature reported a risk of residual shunt

after ligation among children operated for PDA in other areas.

Nevertheless, little is known about the magnitude of residual shunt and associated factors among children for whom PDA ligation done in Ethiopia in general and in the study setting in particular.

1.3. Significance of the Study

The purpose of this study is to evaluate the magnitude of a residual shunt in children presented to our centers for whom surgical management (PDA Ligation) was done so that optimal management options can be recommended for a resource-limited setup. The study will identify the proportion of children who developed residual shunt among surgically-treated children and its contributing factors. Identifying the magnitude of residual shunt will be essential to designing the best management approach, preventive measures, and effective treatment outcomes. Furthermore, the data will be used as a baseline for further studies in the country.

2. LITERATURE REVIEW

2.1. The magnitude of residual shunt among operated children for PDA

There is a continuous debate as to which option of surgical management is optimal (13). In a study done by Nili Zucker et. al in London, patients were evaluated clinically and by color Doppler study after surgical ligation and the finding was around 18% of patients had residual patency by color Doppler while 4.6% of these had continuous murmurs on auscultation. Residual patency of doubly ligated duct may occur because of either recanalization or incomplete occlusion during surgical closure(13,14) and the rate of residual ductal flow was around 2% to 23% in other studies (7,15). The fear of residual shunt or residual patency is that there are reports of infective endarteritis with its sequelae which require endarterectomy and redo percutaneous device closure after PDA ligation(2,3). This also justifies the closure of even asymptomatic silent PDA as a risk of pulmonary endarteritis and infective endocarditis complicated with pulmonary embolization which requires surgical intervention reported in literature (16,17,19).

2.2. Factors associated with residual shunt among operated children

2.2.1. Socio-demographic Characteristics

The underlying factors that cause persistent patency of the ductus arteriosus are not well understood as most cases of PDA are sporadic. In a family having one sibling diagnosed with a PDA, there is around a 3% chance of a PDA in subsequent offspring. The female-to-male ratio for PDA is about 2:1 in most reports, supporting a genetic influence(6), while in another study it is nearly equal(8). In a single-center cross-sectional study previously done at the same institution by Abebe Bezabih, the female-to-male ratio is around 3:1(20). The age distribution at diagnosis varies in different geographic areas with a wide range. In a study done in Yemen, the majority(around 65.5%) are infants with children accounting for around 17.6% and neonates 16.9%(7). In another study, the mean age at operation was 5.5 years, ranging from 0.5 to 17.9 years(4).

Evidence showed that the occurrence of PDA is inversely related to gestational age and weight at birth. In an observational multicenter study done in Turkey, 44% of infants with

PDA was born at <27 weeks gestation, and around 62% of those with PDA weighed <1,000g (7,21).

Age is considered an important predictor for the development of pulmonary hypertension and pulmonary vascular disease (PVD). PDA has a more marked effect on the pulmonary circulation than a ventricular septal defect and those irreversible pulmonary vascular changes may occur usually under the age of two years warranting early intervention(22).

2.2.2. Preoperative Parameters

The clinical presentation of patients with PDA varies from those who are almost asymptomatic to those who present with features of full-blown congestive heart failure. The clinical feature is dictated largely by the size of the left-to-right shunt, which mainly depends on some anatomical and physiological factors. Infants with moderate to large ductus arteriosus may present with signs and symptoms of congestive heart failure, including poor feeding with failure to thrive, tachypnea, diaphoresis, failure to thrive, generalized body swelling, recurrent respiratory infection within the first few weeks of life as the left-to-right shunt increases with falling pulmonary vascular resistance immediately after birth. More commonly, many PDAs are diagnosed by echocardiogram done incidentally for another condition or during evaluation for an asymptomatic "machinery" murmur. Some relatively healthy children may complain of exercise intolerance upon thorough evaluation(7,9).

Echocardiography is used for confirmation, even though ECG and CXR may give some clues about the hemodynamic impact of PDA. There will be left atrial and left ventricular enlargement due to volume overload. The degree of ductal shunting is estimated by measuring the ratio of the left atrium size to the aortic root size during systole with the normal range being 0.8-1.0. There is a significant left-to-right shunt with left atrial enlargement if this ratio is greater than 1.2(6). Children with hemodynamically significant PDA may present with overt heart failure from the outset if not intervened early(9).

Regarding PDA diameter from transthoracic Echocardiography in the study done in Yemen children for whom PDA intervention was done, around 53.4% of patients had moderate PDA, 29.7% patients had a large PDA, and around 16.9% of them had a small PDA(7).

2.2.3. Post-operative Parameters

Closure of hemodynamically significant PDA should be considered as standard of care in the management of PDA as early as possible either by surgical or transcatheter methods if presented late or following failure of medical management. However, Closure of the very small, hemodynamically insignificant PDA is controversial. But closure of such defect is

recommended to eliminate or reduce the risk of infective endocarditis (IE) and infective endarteritis and embolic phenomena(3,15).

Transcatheter PDA closure has almost replaced surgical ligation of the PDA in the past 2-3 years in Europe particularly in Germany and France even for extremely preterm infants, with the transcatheter methods becoming the primary therapy in the major centers instead of the previous practice of failed medical therapy(10).

In a study done in Pakistan by Arif Zulqarnain et al, the cost of PDA device closure was 16.52% higher than the cost required for surgical ligation despite a lower complication rate and less hospital stay in the device closure group. Percutaneous device closure also requires a significant level of expertise and well quipped Cath lab setup (23).

Pulmonary arterial hypertension was diagnosed by Echocardiography in all patients intervened surgically, with around 61.0% presenting with moderate to severe PAH and 39.0% having mild to moderate pulmonary hypertension. Most of the patients(78.6%) were extubated in the ICU after surgery and ICU stay was more than 12 hours in around 71.0% of patients(7).

The relationship between ductal size and severity of pulmonary hypertension was assessed and the finding showed that those children with moderate and large-sized ducts tend to have moderate and severe pulmonary hypertension respectively compared with those with small PDA(22).

PDA surgical intervention is a relatively safe procedure with good outcomes. In a study done in Yemen, post-operative complications were found in 7.2% of patients of which residual duct problem was the commonest complication in 28.6% followed by injury to the recurrent laryngeal nerve in 19.0%. In this study, hospital mortality was around 1%. The majority (90.3%) of the patients were discharged on the fifth day or earlier. Patients with moderate to severe pulmonary hypertension and those with post-operative complications were significantly associated with longer hospital stays of more than 5 days and delayed extubation in the ICU(7).

A 12-year retrospective study done by Mehmet Tort et al. to assess the outcome of surgically treated patients with PDA showed that pulmonary hypertension was diagnosed in 96.0% of patients. Pulmonary artery (PAP) was higher preoperatively in patients with associated other congenital heart diseases compared to those diagnosed with isolated PDA(8).

There is a fear that surgical management worsens surgical outcomes in those children with severe pulmonary artery hypertension. Those patients may need cardiac catheterization or a test for response to pulmonary vasodilators to proceed with surgical intervention. A study done by Alberto Rangel et al showed that there was significant improvement in Pulmonary artery pressure after Surgical management of PDA(14).

The study done in Yemen by Nabeel et al. showed that patients with moderate to severe pulmonary hypertension are more likely to have longer ICU stays, higher postoperative pulmonary hypertension-related complications and worse outcomes in terms of morbidity and mortality compared to those with mild pulmonary artery hypertension(7).

2.3. CONCEPTUAL FRAMEWORK

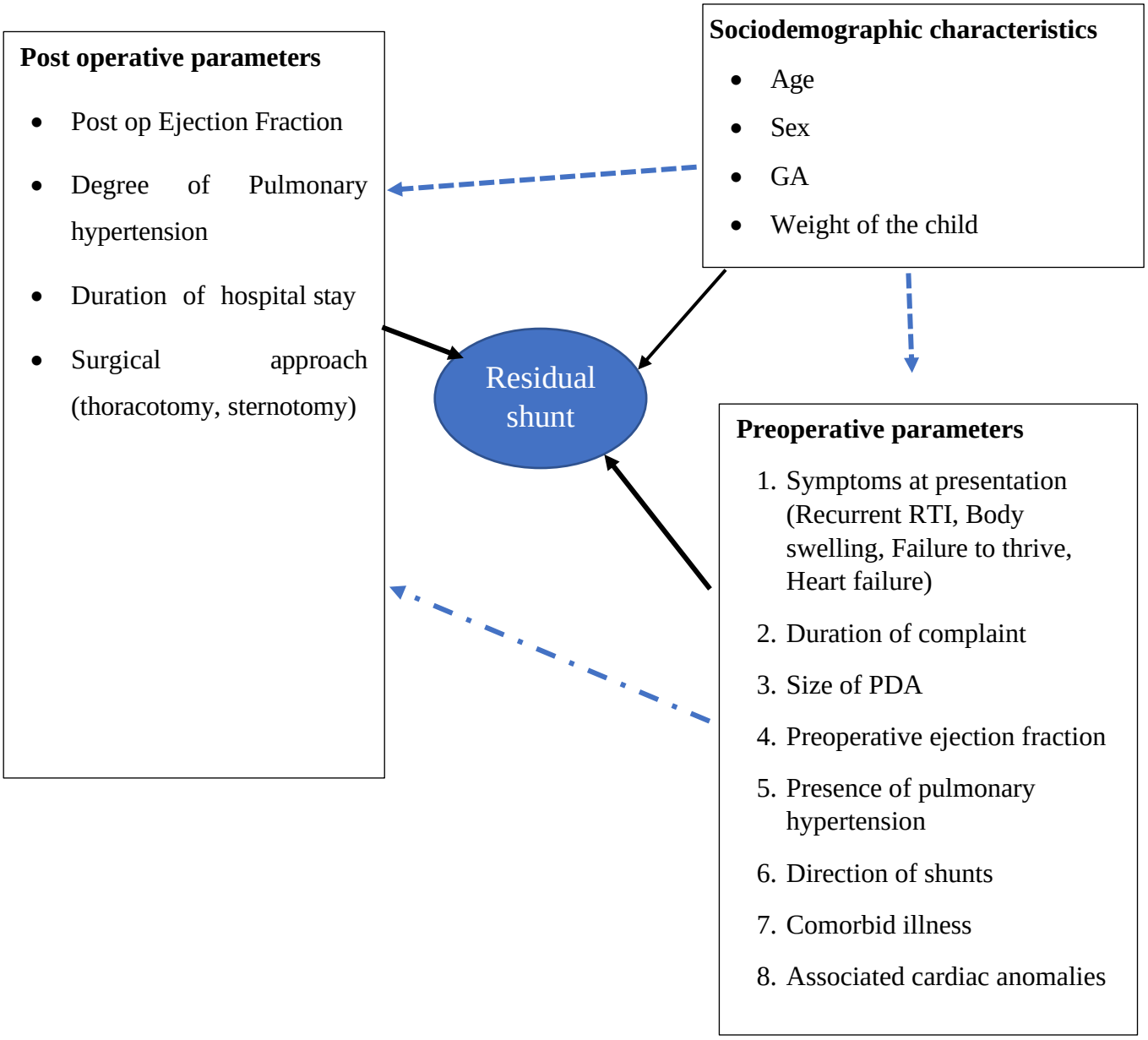

Figure 1:Conceptual Framework developed from the literature review for the study on the magnitude of residual shunt among operated children for PDA at Tikur Anbessa Specialized Hospital and Cardiac Center of Ethiopia, 2024

3. OBJECTIVES

3.1. General objective

- To assess the magnitude of residual shunt and associated factors among surgically treated children for patent ductus arteriosus at Tikur Anbessa Specialized Hospital and Cardiac Center, Addis Ababa, Ethiopia,2024.

3.2. Specific objectives

- To determine the magnitude of residual shunt among surgically treated children for patent ductus arteriosus at Tikur Anbessa Specialized Hospital and Cardiac Center, Addis Ababa, Ethiopia, 2024.
- To identify factors associated with residual shunt among surgically treated children for patent ductus arteriosus at Tikur Anbessa Specialized Hospital and Cardiac Center, Addis Ababa, Ethiopia, 2024.

4 METHODOLOGY

3.3. Study Setting and Period

The study was conducted from April to June 2024 at Tikur Anbessa Specialized Hospital (TASH) and Cardiac Center of Ethiopia (CCE), both of which currently give comprehensive care for cardiac patients.

TASH, established in 1964, is a public teaching hospital of the Addis Ababa University-College of Health Sciences It is the largest referral hospital in the country with around 700 in-patient beds and separate 20 Cardiothoracic surgery beds. TASH has an echocardiography service, a cardiac catheterization laboratory, a computerized tomography scanner, one dedicated operating room for cardiac surgery, and a cardiac intensive care unit(ICU) with a capacity of 12 beds.

CCE is a charity organization that is currently giving mainly comprehensive cardiac care. It was established in 2009 and its services were initially mission-based but since 2017 the center started entire services with the local team. Currently, it has two dedicated operating rooms and 4 cardiothoracic surgeons with 10 separate cardiac ICU beds. All cardiac services are given for free and the center is funded mainly through public and NGO donations.

3.4. Study design

A hospital-based cross-sectional study design was used by reviewing the medical records of children operated for patent ductus arteriosus at TASH and CCE between January 1, 2021 to December 31, 2023.

3.5. Source and Study Population

The source population was all children who were operated on for PDA surgery at TASH and CCE between January 1, 2021 and December 31, 2023.

The study population was all children who were operated for PDA at TASH and CCE between January 1, 2021 and December 31, 2023 and who fulfilled the eligibility criteria of the study.

3.6. Inclusion and Exclusion Criteria

All children (18 years or younger (who were operated for isolated PDA by ligation surgical methods and had complete documents were included in the study.

Children who were operated for PDA by division and closure surgical methods, PDA banding, and those who had incomplete records on the major outcome and exposure factors were

excluded from the study.

3.7. Sample size determination

A single population proportion formula was used to calculate the sample size for the study participants using the following assumptions: 50% of the proportion of assumed residual shunt among children operated for PDA because of the absence of local study on a similar topic, 1.96 critical value at 95% confidence interval and 5% of margin of error.

- n= $\frac{Z_{\frac{\alpha}{2}}^2 P(1-P)}{d^2}$
- $n = \frac{(1.96)^{2(0.5)(0.5)}}{(0.05)^2}$=384

Where

-P= the Assumed proportion of residual shunt

d =the margin of error 5%.

Z α/2= Critical value at 95% confidence interval (1.96)

- n-required minimum sample size

Since the source population of patients that had undergone PDA surgery during the study duration was less than 10,000(N=237 PDA surgeries), a finite population correction formula was used to correct the sample size using the following formula;

Nf=$\frac{n_0}{(1+\frac{n_0}{N})}$=147

. After adding, 15 % for the nonresponse rate, the total sample size was 169.

3.8. Variables

3.8.1. Outcome variable

Residual shunt (Yes vs. No)

3.8.2. Exposure variables

- Social demographic factors: Age at surgery, sex, weight
- Pre-operative parameters: Gestational age at delivery, Clinical presentation, Duration of Complaint, the size of PDA, Ejection Fraction, pulmonary Hypertension, direction of shunt, associated Congenital Cardiac disease, comorbid illness
- Post-operative parameters: Estimated blood loss, duration of surgery, postoperative complications, cardiac ICU admission, duration of Cardiac ICU stay, post-operative EF, post-operative degree of Pulmonary hypertension
- Surgery done: Ligation

3.9. Operational definitions

PDA ligation: Tying or ligating PDA by using a double silk stitch near the Aortic and Pulmonic side without transection after dissecting PDA and RLN is excluded from the field. This also includes adding hemoclips in between the two silk sutures used for simple ligation

PDA division: the ductus arteriosus is dissected around and encircled, cross-clamp is applied at both aortic and pulmonic sides of PDA for bleeding control and followed by transection of the midpoint of PDA and closure of both ends using proline 5-0 or 4-0.

Residual shunt: the presence of color flow on color Doppler echocardiography at the PDA site

Pulmonary hypertension: pulmonary artery systolic pressure of 30 mmHg will be taken as pulmonary hypertension using Transthoracic echocardiogram (TTE), which remains the most important non-invasive screening tool though right heart catheterization is considered the gold standard for the diagnosis of Pulmonary hypertension(22).

- **Mild** if pulmonary artery systolic pressure is 30–50 mmHg
- **Moderate** if pulmonary artery systolic pressure is 51–65 mmHg
- **Severe** if pulmonary artery systolic pressure is ≥ 65 mmHg

The assessment of the size of the patent ductus arteriosus is done by using two-dimensional or Doppler interrogation Echocardiography**.** There is a Proposed staging system (adapted from McNamara and Hellman, unpublished clinical triaging system for ligation of a patent ductus arteriosus (PDA)) for determining the magnitude of the hemodynamically significant ductus arteriosus (HSDA). It is based on clinical and echocardiographic criteria(24).

- **Insignificant or small size PDA** was taken as the diameter of patent ductus arteriosus of 1–1.5 mm
- **Moderate size PDA** was taken as the diameter of patent ductus arteriosus of 1.5-3 mm
- **Large size PDA** is taken as the diameter of patent ductus arteriosus of more than and equal to 3 mm

3.10. Data collection tool and Quality assurance

Data on socio-demographic, clinical presentation, pre-operative, and post-operative parameters were extracted from the medical records of the patients using a structured electronic abstraction tool. Data was collected by four trained data collectors, senior general surgery residents with the supervision of two cardiothoracic surgery fellows. Training on the objective of the study and data collection tool was given to the team for one day on April 01, 2024. To further assure data quality, data was cleaned by checking for inconsistencies, numerical errors, and missing parameters. Where discrepancies are observed, the data entered was verified with the primary

data source.

3.11. Data management and analysis

Data were collected using electronic tools, coded, and exported into SPSS version 25 for data management and analysis. Sociodemographic and clinical characteristics were described using descriptive summary measures. The results were presented in Frequency tables with percentages. Continuous variables were summarized by using measures of central tendency and dispersions based on the nature of the data.

A bivariate logistic regression analysis was run to see the association between independent and outcome variables. Independent variables that had a P-value <0.25 were considered as a candidate for multivariate logistic regression analysis. Therefore, multivariate logistic regression analysis was conducted to assess the associations between independent variables and residual shunt after controlling for potential confounders. The strength of associations was estimated by adjusted odds ratio (AOR) with its 95% confidence interval. Statistical significance was declared at a p-value <0.05. The final model's adequacy was tested using the Hosmer and Lemeshow test, and the result showed that the data fitted the model very well (X2(8) =3.50 and p-value=0.899). Multicollinearity between independent variables was controlled using the variance inflation factor (VIF<10).

3.12. Ethical Considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of the Faculty of Medicine, Addis Ababa University College of Health Sciences with cooperation letters to be written to the medical recording department of Tikur Anbessa Specialized Hospital and Cardiac Center of Ethiopia. Since the study was conducted using already recorded data for clinical purposes, a waiver of consent was also obtained from the IRB on behalf of the patients to be included in the study. The medical record number was used for the data collection and personal identifiers of the patient were not used in the research report. Access to the collected information was limited to the research team and confidentiality was maintained throughout the project.

3.13. Dissemination plan

The findings of this study will be disseminated to Addis Ababa University College of Health Sciences, the Department of Surgery, public health, and other bodies that need the findings to use as baseline data for another study or possible program planners for intervention measures. Furthermore, the findings will be submitted for publication in a reputable peer-reviewed journal.

4. RESULT

4.1. Socio-demographic characteristics and pre-operative parameters

A total of 167 participants were included in this study. The median (± interquartile range) age of the participants was 4.2(± 5.0) years. Among the study participants, 112(67 %) were females (Figure 2).

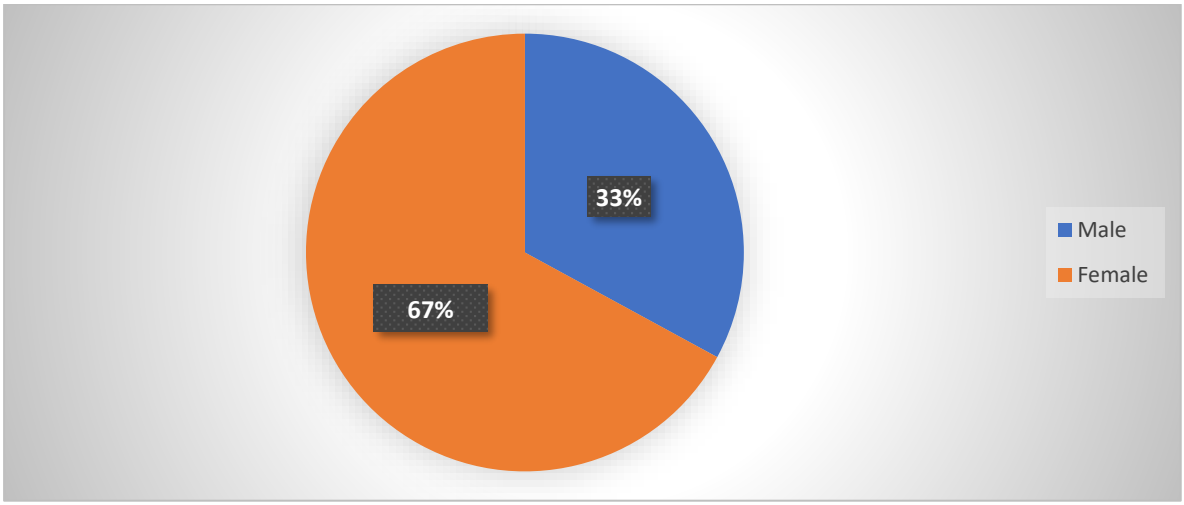

Figure 2:Sex distribution of children for whom PDA ligation was done at TASH and CCE in Ethiopia between January 1, 2021 and December 31, 2023 (n=167).

4.2. Preoperative Parameters

The study showed that 123(73.7%) children with PDA had different symptoms during presentation for consultations, of which 28(16.8%) experienced symptoms since birth. Accordingly, 65 (38.9%) and 39(23.4%) had recurrent respiratory tract infections and shortness of breath respectively. Pulmonary hypertension was documented among 75(44.9%) children. In addition, 47(28.1%) children with PDA had different kinds of comorbidities. Down syndrome was diagnosed in 19(11.4%) children with PDA. Furthermore, 16(9.6%) had cough, 9(5.4%) irritability and 17(10.2%) had diaphoresis. Besides, the median (± IQR) weight of the children was 14 (±9) kilograms. On the other hand, 31(18.6%) children had weight loss. On average, the PDA size during the consultation was 5.10(± 0.14) millimeters with an ejection fraction of 67.5(±0.4) percent. In stratified analysis, the size of PDA was 5.27(±1.8) millimeters in males and 5.11(±1.8) millimeters in female children (P-value=.534) Among those patients for whom PDA ligation was done, 47 (28.1%) had one or more comorbid illnesses of which Down syndrome was the commonest associated anomaly in 19(11.4%) children. Regarding the direction of residual shunt and associated cardiac anomalies, 160(95.8%) had left to right shunts while 20(12.0%) children with PDA had associated ventricular septal defects (VSD) (Table 1).

Table 1: Preoperative parameters of children who have undergone surgical treatment for isolated PDA at TASH and CCE in Ethiopia between January 1, 2021 and December 31, 2023 (n=167)

Variables	Frequency	Percent
Symptomatic at presentations		
No	44	26.3
Yes	123	73.7
Recurrent respiratory infections		
No	102	61.1
Yes	65	38.9
Shortness of breathing		
No	128	76.6
Yes	39	23.4
Cough		
No	151	90.4
Yes	16	9.6
Weight loss		
No	136	81.4
Yes	31	18.6
Irritability		
No	158	94.6
Yes	9	5.4
Palpitation		
No	164	98.2
Yes	3	1.8
Failure to thrive		
No	163	97.6
Yes	4	2.4
Body swelling		
No	164	98.2
Yes	3	1.8
Feeding interruption		
No	132	79.0
Yes	35	21.0
Easy fatigability		
No	147	88.0
Yes	20	12.0
Diaphoresis		
No	150	89.8
Yes	17	10.2
Fever		
No	164	98.2
Yes	3	1.8
Pulmonary hypertension		
No	92	55.1
Yes	75	44.9
Direction of shunt		
Left to Right	160	95.8
Bidirectional	7	4.2
Types of associated cardiac diseases		
VSD	20	12.0
Others*	15	8.98

* ASD, patent foramen Ovale, COA. CRHD, Double superior venacava, VSD and ASD, etc.

5.3 Type of Surgery

The surgical approach for PDA is mainly done through posterolateral thoracotomy through the third or fourth intercostal space unless anatomic or other cardiac conditions force it to go in through median sternotomy. In this study, PDA surgery was done through left posterolateral thoracotomy for 154 (92.2%) of children. All surgical procedures were performed by ligation with an average operation time of 91(± 48.8) minutes.

4.3. Post-operative parameters and outcome

Overall, 123(73.7%) children had immediate postoperative complications of which 128(76.6%) had hypertension and 49(29.3%) had hypokalemia. A total of 160 (95.8%) operated children required ICU admission following surgery, with an average length of stay of 2.28 (+1.07) days. The total length of hospital stay on average was 5.62 days (±2.62) days. All operated children were discharged with improvement (Table 2).

Table 2:post-operative parameters and outcome of patients who have undergone surgical treatment for isolated PDA at TASH and CCE in Ethiopia between January 1, 2021 and December 31, 2023 (n=167)

Variables	Frequency	Percent
Post operation complications		
No	44	26.3
Yes	123	73.7
Hypertension		
No	39	23.4
Yes	128	76.6
Hypokalemia		
No	118	70.7
Yes	49	29.3
Bleeding		
No	162	97.0
Yes	5	3.0
Metabolic acidosis		
No	160	95.8
Yes	7	4.2
ICU admission		
No	7	4.2
Yes	160	95.8

5.5. Magnitude of residual shunt among children operated with PDA

Postoperative Echocardiography was done for all patients for whom PDA surgery was done upon discharge from the hospital. There was no residual shunt in patients for whom PDA division and closure were done as there was a complete interruption of flow across the ducts after division. However, from the 167 children operated for PDA and surgical ligation was done, a residual shunt was detected in 37 cases making the post-operative magnitude of the residual shunt 22.2% (95% CI= 16.2%-28.1%) **(Figure 3).**

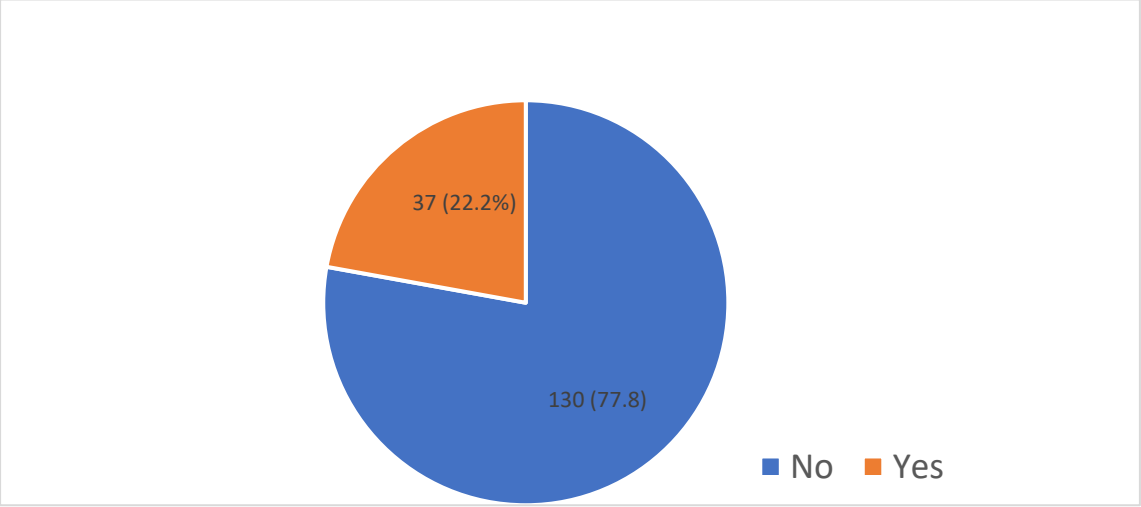

Figure 3:The magnitude of residual shunt among children who have undergone surgical treatment for isolated PDA at TASH and CCE in Ethiopia between January 1, 2021 and December 31, 2023 (n=167)

5.6. Factors associated with residual shunt

In bivariate analysis, sex, weight loss, being symptomatic at presentations, age of the children, size of PDA, and presence of pulmonary hypertension had a P-value <0.25 and were selected as a candidate for multivariable logistic regression analysis. However, at multivariate logistic regression analysis, only the presence of pulmonary hypertension showed a statistically significant association with residual shunt among children operated for PDA with surgical ligation.

Accordingly, children who had pulmonary hypertension were 2.80 times (AOR=2.80, 95% CI: 1.265, 6.222) more likely to develop residual shunt after ligation for PDA compared to children who had no pulmonary hypertension before surgical intervention **(Table 4).**

Table 3: Factors associated with a residual shunt in children who undergone surgical treatment for isolated PDA at TASH and CCE in Ethiopia between January 1, 2021 and December 31, 2023 (n=167)

Variables	Residual shunt		COR (95% CI)	AOR (95% CI)	P-value
	Yes	No			
Weight loss at presentation					
No	33	103	1	1	
Yes	4	27	.46(.151,1.418)	0.48(0.145,1.622)	0.240
Sex					
Male	16	39	1		
Female	21	91	.56(.265,.192)	0.66(0.295, 1.495)	0.323
Symptomatic at presentation					
No	13	31	1	1	
Yes	24	99	.57(.263,1.269)	1.81(0.748, 4.407)	0.188
Pulmonary hypertension					
No	14	78	1	1	
Yes	23	52	2.46(1.162,5.224)	2.80(1.265, 6.222)	**0.011**
Age of children				1	
6 months to 2 years	8	32	1	1	
2-5 years	9	51	.70(.247,2.017)	.88(.290,2.716)	0.835
6-12 years	18	40	1.80(.619,4.672)	2.04(.734,5.724)	0.172
12-18 years	2	7	1.14(.198,6.590)	.92(.139,6.124)	0.933
PDA size in mm					
1.5-3 millimeters	4	30	1	1	
>=3 millimeters	33	100	2.47(.812,7.548)	2.27(0.703, 7.377)	0.170

5. DISCUSSION

The current study was conducted to assess the prevalence of residual shunt and associated factors among 167 surgically treated children for a diagnosis of isolated Patent ductus arteriosus at Tikur Anbessa Specialized Hospital and Cardiac Center in Ethiopia between January 1, 2021, and December 31, 2023.

Among the study participants, 112(67 %) were females with a 2 to 1 female-to-male ratio. This is almost similar to findings from a local study which is a 3 to 1(20) and studies done in other settings with 2 to 1 (7,25) which may be likely due to observed demographic trends.

The median (± interquartile range) age of the participants at PDA diagnosis was 4.2(± 5.0) years and 123 (73.7%) were symptomatic at diagnosis. This is a late presentation compared with other studies in which most of the study participants were infants(65.5%), followed by children (17.6%)(7). Delayed presentation was found to be associated with a significantly increased risk of congenital heart disease(7,26). Surgical ligation of the PDA in preterm infants three weeks earlier results in more favorable outcomes in early initiation of enteral nutrition and earlier recovery from ventilation compared to delaying PDA closure by three weeks(27).

The rate of residual shunt or residual patency varies worldwide after surgery and most current PDA management is shifting towards percutaneous trans-catheter methods in the developed world. In our study, the post-operative prevalence of residual shunt among children for whom PDA ligation was done was 22.2% (95% CI= 16.2%-28.1%) (7). This is from echocardiography done for all patients upon discharge from the hospital after recovery. This is significantly higher than the recent study done in Yemen in which the rate of residual shunt was 2.1% among children for whom PDA simple ligation (16.2%) and PDA ligation with hemoclip application (82.1%) were done. In this study, the majority of them were infants(65.5%), followed by children (17.6%)(7). This difference may be because of additional modification on simple ligation with hemoclip application which decreased magnitude but did not completely avoid residual shunt in addition to earlier age at intervention. PDA ligation is considered a palliative option of management as even after double or triple ligation, 22% of patients had residual patency and required redo division of PDA to completely avoid the question of recanalization or residual patency(14). There are different varieties of ligation which could be simple ligation, ligation with hemoclips application, double Clip application, or Double ligation with additional transfixion. These modifications are attempted to minimize the risk of residual shunt. In another study in which double ligation with additional transfixion was done, the rate of residual shunt was found to be 3.1%(4) as compared to previous results with only double ligation in which the rate of residual shunt was 4.6% on clinical

cardiovascular examination and 18% on color Doppler Echocardiographic examination which is more sensitive than clinical examination. Even though those patients with residual shunt were not followed longer, they remain at risk of infective endarteritis and its sequelae if not intervened. For those patients with a residual shunt on follow-up Echocardiography after a mean follow-up of 24±34 months, transcatheter device closure for some, and surgical division was attempted for others to avoid long-term complications (13). In another study, the rate of residual shunt after ligation was 23% despite the disappearance of ductal thrill checked intraoperatively after ligation. Color Doppler assessment was done after a median follow-up of 4 months (range of 1 to 13 months). Other alternate methods were using intraoperative color flow echocardiographic assessment to decide on whether to add additional ligature or division of the duct if residual patency is detected after double ligation (15). These discrepancies occur likely because ligation is prone to subjective bias as to the adequacy of ligature which needs the balance between loose ligature causing residual patency and tight ligature with the risk of rupture causing torrential hemorrhage. In a resource-limited setup like ours where medical management is not practical in addition to almost absence of routine percutaneous intervention (only mission-based), the only long-lasting management we have in a few centers as a country is surgical intervention, the one that should better avoid residual shunt with its long-term sequelae to be taken as the standard of care. So, the division and closure technique is better taken as the surgical management of choice to possibly avoid the risk of endarteritis, pulmonary embolism, and stroke with additional cost to the family due to repeated admissions.

Pulmonary hypertension was diagnosed in 75(44.9%) patients, which is significantly higher than the finding (5.5%) from the South Carolina Medical Center in which the average age at PDA diagnosis was 0.7 years (5). This may be because our patients were intervened late so that higher proportion of them developed pulmonary hypertension by the time they came for intervention. Our finding has a nearly similar result to the study done in Yemen in which 61% of children Operated for PDA have at least moderate Pulmonary hypertension(7) and 60.2% of children with PDA have pulmonary hypertension in Nigeria(22).

The only factor that significantly affected the development of residual shunt in this study was the presence of pulmonary hypertension. Accordingly, having pulmonary hypertension was associated with almost three-fold increased odds of having residual shunt than patients with no pulmonary hypertension. The study done in Yemen has shown similar results in which pulmonary hypertension is associated with an increased risk of postoperative complications including residual shunt(7).

The mean PDA size is 5.2mm with a minimum of 1.5mm and a maximum of 10mm. This is higher than the finding in Nigeria in which the mean ductal size is 3.78mm with a minimum of 1mm and a maximum of 10mm(22). Regarding the size of PDA, 53.4% had a moderate diameter, whereas 29.7% had a large diameter in Yemen, which is different from ours in which 79.6% had a large PDA(7). Again, the larger size of the PDA might have contributed to a higher magnitude of the residual shunt in high our center.

Hypertension (76.6%%), Hypokalemia (29.3%), and residual shunt (22.2%) were the top postoperative complications detected in this study. Hypertension might have happened due to post-thoracotomy pain, aortic manipulation, or due to surgery-induced traumatic neurohormonal factors which are required to be controlled by medications before discharge. It is usually transient, but with a detrimental immediate postoperative effect like bleeding if not controlled well, that can be normalized within a short duration to the extent of being free of any antihypertensive medications(28).In another study, residual shunt was documented as the commonest post-operative complication in Yemen followed by recurrent laryngeal nerve injury(7).

Limitations of the study

This study assessed only the short-term outcome and associated factors of the PDA closure without considering the longer-term surgical complications. Furthermore, the evaluation of pulmonary hypertension based on echocardiographic measurements presents limitations, including the risk of misinterpreting postcapillary pulmonary hypertension as a pulmonary arterial hypertension. Furthermore, low sample size may affect the determination of other factors that may contribute to the development of residual shunts.

5.1. CONCLUSION

The magnitude of residual shunt in those patients for whom PDA ligation was done was significantly high in our setup. Preoperative pulmonary hypertension was an independent determinant of residual shunt among children operated for PDA using surgical ligation.

6. RECOMMENDATION

It is advisable to perform PDA division and closure instead of ligation to avoid the risk of residual shunt particularly in a resource-limited setup where percutaneous options of management for redo intervention are not well practiced. It is better to avoid ligation surgical intervention for children with PDA who have preoperative pulmonary hypertension. In addition, children who developed residual shunt should be followed for possible long-term residual shunt-related complications. Further study is required with a better study design and larger sample size to assess potential determinants of residual shunt among children operated with ligation surgical method for patent ductus arteriosus.

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ANNEX I: QUESTIONNAIRE

Magnitude of Residual Shunt among Surgically treated patients with Patent Ductus Arteriosus at Tikur Anbessa Specialized Hospital and Cardiac Center of Ethiopia

Hospital A. Tikur Anbessa Specialized Hospital

B. Cardiac Center of Ethiopia MRN___

Phone Number_____

1. Sociodemographic characteristics

A.) Age_____

B.) Sex_____

2. Preoperative Parameters

II) At birth the child is

A) Term

B) Preterm

III) Clinical Presentation (multiple options possible)

A) Irritability

B) Shortness of breath

C) Cough

D) Body swelling

E) Recurrent Respiratory Infection

F) Weight loss

G) Infective endocarditis

H) Other/s, _____

IV) Duration of Complaint_____

V) The weight of a child in Kg_____

VI) The size of PDA in mm_____

VII) Ejection Fraction in %_____

VIII) Pulmonary Hypertension

A) Yes

B) No

IX) If yes to the above question, the degree of Pulmonary Hypertension

A) Mild

B) Moderate

C) Severe

X) Direction of shunt

A) Left to Right

B) Right to left

C) Bidirectional

XI) Associated Congenital Cardiac disease

A) Yes

B) No

XII) If yes to above question, specify_____

XIII) Associated other congenital anomalies

A) Yes

B) No

XIV) If yes to the above question, specify_____

XV) Echocardiography

A) Transthoracic

B) Transesophageal

3. Postoperative Parameters

XVI) Surgical Approach

A) Left thoracotomy

B) Median sternotomy

C) Right thoracotomy

XVII) Surgery done

A) Ligation

B) Division and Closure

XVIII) Estimated blood loss in mm_____

XIX) Duration of surgery in minutes_____

XX) Post operative complications

A) Bleeding

B) Hoarseness of voice (RLN injury)

C) Chylothorax

D) Pneumothorax

E) Pneumonia

F) Hypertension

G) Surgical site infection

H) Recurrence

I) Other, _____

XXI) Cardiac ICU admission

A) Yes

B) No

XXII) Duration of Cardiac ICU stay in days_____

XXIII) Total hospital stays in days_____

XXIV) The presence of Residual Shunt

A) Yes

B) No

XXV) Grading of Residual Shunt

A) Mild

B) Moderate

C) Severe

XXVI) Comorbid illness

A) HIV

B) Diabetes Mellitus

C) Hypertension

D) Bronchial Asthma

E) Other, Specify_____

XXVII) Post operative EF (%) _

XXVIII) Post operative degree of Pulmonary hypertension

A) Mild

B) Moderate

C) Severe

XXIX) Outcome

A) Improved

B) Died