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An overview of treatment for atrial septal defect with pulmonary hypertension

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Abstract

21 **Background:** Atrial Septal Defect (ASD) is a congenital heart defect which can be the cause of comorbidities in the form of Pulmonary Arterial Hypertension (PAH) and therapy cannot be done simply by correcting the ASD but requires further study and evaluation.

Purpose: Describe the treatment given to patients with ASD and PAH and the correlation between the administration of interventional therapy and the patient's probability of PH.

Method: This study is a descriptive quantitative using a cross-sectional research design. The sampling technique was total sampling method. The samples were 41 ASD patients with PAH at Prof. Ngoerah General Hospital in Denpasar in 2022. Patients under 18 years of age and those with other congenital heart disease will be excluded. The demographic characteristics assessed were the patient's age and gender. The therapy data included information on medical therapy and intervention therapy.

Results: Focus of medical therapy was supportive therapy rather than specific PAH therapy. Percutaneous ASD closure was the most widely-used intervention therapy compared to surgical ASD closure. Based on statistical analysis, the p value > 0.05 is 0.284, so there is no significant correlation between the probability of the patient's PH and the provision of intervention therapy.

Conclusion: At Prof Ngoerah General Hospital Denpasar, the majority of ASD patients with complications of pulmonary hypertension were females aged between 21 to 30 years. The medical therapy given is adjusted based on the severity of PH as assessed through echocardiography examination. Majority of patients received supportive therapy compared to specific therapy for PAH. Medical therapy is prioritized for patients who have contraindication criteria for interventional therapy. Percutaneous ASD Closure was found to be the largest percentage in interventional therapy regardless of the severity, except for patients who were indicated to undergo surgical ASD closure. There is no significant relationship between the patient's PH probability level and the choice of intervention therapy.

26 **Keywords:** Atrial Septal Defect (ASD); Patients; Pulmonary Arterial Hypertension (PAH).

INTRODUCTIONS

Atrial septal defect (ASD) is a condition that causes a hole between the walls of the right and left atria. One of the causes of this condition is incomplete closure of the foramen ovale after birth or due to another hole in the wall between the two atria during pregnancy (Asmayadi, 2018). This disease is an acyanotic heart disease with a presentation of 10% of all congenital heart diseases in adult

6 patients. Globally, the overall prevalence of diagnosed ASD is estimated at 3.89 per 1000 children and 0.88 per 1000 adults and the estimated incidence is 56 in 100,000 live births (Martin, Shapiro, & Mukherjee, 2015). Meanwhile, the incidence of sufferers of congenital heart disease such as ASD in Indonesia reaches 8 per 1000 live births (Munaiseche, Munayang, & Kaulang, 2016).

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15

There are several types of ASD which determined by the location of the hole in the atrial septum, including ostium secundum with an incidence of 85%, ostium primum with an incidence of 10%, sinus venosus with an incidence of 5%, and coronary sinus defect, which are relative rare (Kurniawaty & Baskoro, 2016).

Young adults with ASD often have comorbidities such as pulmonary hypertension, respiratory infections, arrhythmias, and other cardiovascular diseases (Kurniawaty & Baskoro, 2016), which will discuss further regarding pulmonary hypertension. Pulmonary hypertension itself is a hemodynamic disorder characterized by a 20 mmHg increase in pulmonary artery pressure at rest (Hoepfer, Ghofrani, Grünig, Klose, Olschewski, & Rosenkranz, 2017). Pulmonary hypertension is divided into five types, depending on the method treatment and the cause. These include pulmonary arterial hypertension, pulmonary venous hypertension, pulmonary hypertension associated with respiratory failure or hypoxemia, pulmonary hypertension due to thrombotic or embolic disease, and hypertension due to diseases affecting the pulmonary blood vessels. As explained, pulmonary hypertension is one of the comorbidities found in patients with coronary artery disease, and this type of pulmonary hypertension is pulmonary arterial hypertension (Simonneau, Montani, Celermajer, Denton, Gatzoulis, Krowka, Williams, & Souza, 2019).

When treating patients ASD, comorbidities such as pulmonary hypertension, supraventricular tachycardia, and left ventricular diastolic dysfunction should be considered. Apart from providing anticongestive medical therapy for ASD, vasodilators are also given to treat high blood pressure. Meanwhile, the closure procedure in ASD patients with pulmonary hypertension is very risky, due to serious complications that can occur after the procedure. Therefore, comprehensive disease management and evaluation are necessary to minimize risks and achieve better outcomes (Habibah, 2018).

4

RESEARCH METHOD

This research uses a cross-sectional retrospective descriptive research method. Carried out at Prof. I.G.N.G Ngoerah General Hospital

2
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1
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Denpasar Medical Records section for nine months starting from January 2023 – September 2023. The clinical variable that will be studied as secondary data is the type of treatment in ASD patients with complications of Pulmonary Hypertension. The accessible population in this study consisted of outpatients with ASD and pulmonary hypertension who visited the integrated heart care clinic Prof.Dr.I.G.N.G. Ngoerah Regional Hospital in January-December 2022. The sampling technique used the total sampling method with the number of samples obtained being 245 patients. Among the 245 patients, 74 had ASD in adult patients, and the remaining 167 had ASD in children. The final sample in this study consisted of 41 individuals, selected based on the inclusion and exclusion criteria that included patients who were 18 years of age or older and did not have any other congenital heart condition that causes pulmonary hypertension.

The independent variable in this study was ASD patients complicated by pulmonary hypertension and the dependent variable was the type of treatment given. Atrial Septal Defect is a condition where there is a defect in the interatrial septum whose diagnosis is confirmed by heart specialist. Pulmonary hypertension is an increase in pulmonary artery pressure above 20 mmHg at rest or above 30 mmHg when carrying out activities, the diagnosis of which is confirmed by a cardiologist. Therapeutic data collection will be adjusted to patient groups based on the level of severity based on echocardiography examination data, namely the possibility of low, moderate and high pulmonary hypertension. Medical therapy is conventional therapy by administering drugs to ASD patients with PAH, medical therapy is categorized into 2, namely 1). Pulmonary vasodilators are drugs that work by relaxing the smooth muscles in the walls of blood vessels, thereby causing widening or dilating of the blood vessels. Several classes of drugs used as pulmonary vasodilators include: prostanoids, endothelin inhibitors, phosphodiesterase inhibitors and Ca channel blockers. 2). Anti-Heart Failure is a drug that functions to increase heart contractions, reduce the heart's workload, and slow the heart rate. Several classes of drugs used as anti-heart failure agents include: Diuretics, Digoxin, ACE inhibitors, β -blockers, and mineralocorticoid receptor antagonists. This therapy data is obtained from medical records

and each therapy will be recorded including the dose and duration of treatment as well as any changes in the patient's therapy. Interventional therapy is an ASD closure procedure either operatively or minimally invasive (percutaneous).

This research has received ethical permission with number No: 367/UN14.2.2.VII.14/LT/2023 issued by the Ethics Commission of the Faculty of Medicine, Udayana University on February 21 2023.

Before entering the editing process, data will be collected first. After that, the data will be processed in several stages, namely editing, coding, data input, and checking the data to ensure there are no errors in data processing. The data that has been collected

will be kept confidential using initials and medical record numbers, and will only be stored on the researcher's computer for one year. In the editing process, the researcher needs to re-check the conformity of the data with the inclusion and exclusion criteria. The data will then be grouped and processed using Statistical Product and Service Solution (SPSS) and will be analyzed descriptively which will then be arranged in the form of a frequency distribution table and analytically to see the correlation and relationship between the probability of PH from the patient and the provision of interventional therapy using the contingency correlation test.

RESEARCH RESULT

4 Table 1. Characteristics of Respondents (n=41)

Variable	Results
Age (Mean \pm SD)(Range)(Year)	(35.66 \pm 3.916)(18-65)
Gender (n%)	
Male	4/9.8
Female	37/90.2
Probability of Pulmonary Hypertension (n%)	
Low	7/17.1
Moderate	16/39.0
High	18/43.9
Types of ASD Closure Interventions (n%)	
Percutaneous	21/51.2
Surgical	2/4.9
Combination	8/19.5
None	10/24.4

Based on the table above, it is known that the calculation of descriptive statistics on the age variable shows that the average age of ASD patients is 35.66 with a minimum of 18 years and a maximum of 65 years. The majority of ASD patients who experience complications of pulmonary hypertension are women, 90.2%.

Based on possibility of PH from echocardiography examination, it shows that of the 41 sample data, the majority were patients with a high probability of PH, 18 people (43.9%), and a moderate probability of PH, 16 people (39%), meanwhile, 7 other patients (17.1%) had a low probability of PH.

Types of ASD Closure Interventions showed that 21 (51.2%) patients underwent percutaneous ASD closure, 2 (4.9%) patients underwent surgical ASD closure, and 8 (19.5%) patients underwent combination ASD closure.

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Table 2. Frequency Distribution of Medical Therapy in Patients with Probability PH

Dose and Type of Drugs	Probability of Pulmonary Hypertension		
	Low (n/%)	Moderate (n/%)	High (n/%)
Ramipril	6/85.7	9/56.2	12/66.7
1x2.5	5/83.3	8/88.8	10/83.3
1x5	1/16.6	1/11.1	1/8.3
2x5	-	-	1/8.3
Bisoprolol	6/85.7	12/56.2	16/88.8
1x2.5	4/66.7	9/75.0	13/81.25
1x10	-	-	1/6.25
1x1.25	2/33.3	5/41.6	3/18.75
1x5	1/16.6	2/16.6	4/25.0
Furosemide	6/85.7	12/75.0	16/88.8
1x40	5/83.3	11/91.6	13/81.25
1x20	1/16.6	2/16.6	4/25.0
2x40	-	-	3/18.75
2x30	-	-	1/6.25
2x20	-	-	1/6.25
Spirolactone	6/85.7	14/87.6	12/66.7
1x25	6/100	13/92.8	11/91.6
1x12.5	-	1/7.1	2/16.7
1x15	-	1/7.1	-
2x25	-	-	1/8.3
Sildenafil	-	3/18.75	8/44.4
3x5	-	-	1/12.5
3x10	-	-	2/25.0
3x20	-	2/66.7	2/62.5
3x40	-	-	2/25.0
3x25	-	1/33.3	-
2x20	-	1/33.3	-
Beraprost	-	1/6.25	8/44.4
3x10	-	-	1/14.8
2x20	-	-	2/28.5
3x20	-	1/100	5/62.5
Propranolol	1/14.2	1/6.25	-
1x10	1/100	-	-
3x10	-	1/100	-
Candesartan	1/14.2	-	3/16.6
1x4	1/100	-	2/66.7
1x8	-	-	1/33.3
Amlodipine	-	-	1/5.5
1x5	-	-	1/100
1x10	-	-	1/100

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3 An overview of treatment for atrial septal defect with pulmonary hypertension

Valsartan	-	-	1/5.5
2x40			1/100
2x80			1/100
Warfarin	-	1/6.25	3/16.6
1x2		1/100	3/100
Aspirin	1/14.2	3/18.75	6/33.3
1x100	1/100	3/100	6/100
Digoxin	-	2/12.5	-
1x0.25		2/100	

Table 3. Correlation between Patient Probability of PH and Types of ASD Closure Interventions

Variable	Types of ASD Closure Interventions				p-value
	Surgical (n=2)	Percutaneous (n=21)	Combination (n=8)	None (n=10)	
Probability of PH (n/%)					
Low	1/50.0	3/14.3	0/0	3/30.0	0.284
Moderate	1/50.0	7/33.3	3/37.5	5/50.0	
High	0/0	11/52.4	5/62.5	2/20.0	

11 From the research results, it is known that medical therapy in patients with a low probability of PH uses a total of 7 types of drugs, namely ramipril, bisoprolol, furosemide, spironolactone, propranolol, candesartan, and aspirin. It was found that 4 out of 7 patients with a low probability of PH received ASD closure, namely 3 people underwent percutaneous ASD closure with a percentage of 14.3% and 1 (50%) person underwent surgical ASD closure.

Medical therapy in patients with moderate probability of PH uses a total of 10 types of drugs, namely ramipril, bisoprolol, furosemide, spironolactone, sildenafil, beraprost, propranolol, warfarin, digoxin, and aspirin. And it is known that the type of ASD closure intervention most frequently used in patients is percutaneous with a percentage of 33.3%.⁹

Medical therapy in patients with a high probability of PH uses a total of 12 types of drugs with more varied types and doses, namely ramipril, bisoprolol, furosemide, spironolactone, sildenafil, candesartan, amlodipine, valsartan, warfarin, aspirin, and beraprost. And the intervention therapy most frequently used in PH patients with a high probability is percutaneous ASD closure with a percentage of 52.4% and combination therapy of both at 62.5%.

The relationship between the probability of PH patients and the type of ASD closure intervention shows that the probability level of PH does not have a significant relationship because the p-value obtained is > 0.05.

DISCUSSION

Demographic Characteristics

According to study findings presented in Table 1, ¹⁸ percentage of ASD with PAH was more in women with a percentage ¹ 90.2%, compared to men which was only 9.8%. The results of this study confirm the results of research that obtained samples from the first adult CHD and pulmonary hypertension registration in Indonesia at Dr. Sardjito General

Hospital, Yogyakarta in 2020, which also stated that the majority of patients were women with a percentage of 78.5% of all patients (Dinarti, Hartopo, Kusuma, Satwiko, Hadwiono, Pradana, & Anggrahini, 2020). Research studied in Vietnam in 2020 revealed that the prevalence of ASD in women (25.9%) was significantly greater than in men

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(16.0%), which provides another evidence to support the findings of this study (Tuan et al., 2020). The majority of ASD patients may be female due to family inheritance or greater susceptibility to genetic mutations. This was clarified in a 2018 study by Aoki and Horie, who noted that while the majority of ASD cases are sporadic, there have been reports of patterns of hereditary inheritance (Aoki & Horie, 2018), with most of the genes that play a role being the NKX2-5 genetic variant. In ASD patients with a family history, the prevalence of the NKX2-5 gene variant can reach 8%, whereas in sporadic cases, it rarely reaches 1-4% (Rozqie, Satwiko, Anggrahini, Sadewa, Gunadi, Hartopo, Mumpuni, & Dinarti, 2022).

The study found that the average age of patients was 35.66, with the youngest being 18 years old and the oldest being 65 years old. These results are similar to those obtained from research conducted in 2020 at Dr. Sardjito Hospital in Yogyakarta, Indonesia, which collected samples from the first adult CHD and CHD-related PH registration. In that study, the average age at which patients were first diagnosed or registered was 34.7 years (Dinarti et al., 2020).

Frequency distribution based on probability of PH from echocardiography examination

Detecting ASD can be challenging due to its non-specific symptoms and sometimes undetectable physical signs, especially in the early stages. A high level of clinical suspicion is required to diagnose the disease before any irreversible pathophysiological changes occur (Bossone, D'Andrea, D'Alto, Citro, Argiento, Ferrara, & Naeije, 2013). Research conducted by Web and Gatzoulis, published in the AHA journal, reveals that many ASD patients either do not exhibit any symptoms or their symptoms are not clear enough, which makes it difficult to identify the age at which symptoms appear (Webb & Gatzoulis, 2006). This is why patients with atrial septal defects (ASD) often delay seeking medical help until they experience symptoms associated with pulmonary arterial hypertension (PAH). As a result, ASD patients at high risk of PH constituted the majority of all ASD patients complicated by pulmonary hypertension who visited Prof Ngoerah Hospital, representing 43.9% of cases (total of 18 patients).

Therapy in patients with low probability of PH

Due to complications from PAH, closure is not a curative treatment for most adult ASDs. Instead, treatment to reduce pulmonary artery pressure is recommended to improve quality of life (Krisdinarti, Hartopo, Anggrahini, Sadewa, Wahab, & Setianto, 2016). The management of patients with PAH requires the use of "supportive therapy" including diuretics and supplemental oxygen, as well as "PAH-specific" pharmacological therapy, according to the CHEST guidelines (Taichman, Ormelas, Chung, Klinger, Lewis, Mandel, Palevsky, Rich, Sood, Rosenzweig, Trow, Yung, Elliott, & Bartsch, 2014). Patients who have a low probability of pulmonary hypertension (PH) usually have a mean pulmonary artery pressure (mPAP) of around 30-50 mmHg, which can still be classified as mild and reversible. The medical therapy given to such patients aims to provide supportive and additional therapy to treat any residual symptoms of PH and maximize the performance of the heart. This is because if the PAP increases by more than 15 mmHg, it can lead to a sudden decrease in right ventricular contractility (Sen, Johns, & Gao, 2019). This statement supports the use of supportive therapy in ASD patients with low probability of PAH, including diuretics, β -blockers, ACE inhibitors, and Angiotensin Receptor Blockers.

In this study, percutaneous ASD closure was the most common interventional therapy given, with 3 out of 7 patients (14.3%) receiving this treatment, while only 1 out of 7 patients (50%) underwent surgical ASD closure therapy. It's important to note that patients with a low probability of PH typically have mPAP values of around 30-50 mmHg, which fall under the mild category and don't require closure. As a result, only a few patients receive interventional therapy, while others are treated with medical therapy, as previously explained. According to a 2020 study by Alkashkari et al., small defects that do not result in excess RV volume are typically not considered for closure. However, if there is evidence of a right-to-left shunt that causes significant hypoxemia and/or paradoxical embolism, closure may be necessary (Alkashkari, Albugami, & Hijazi, 2020). In patients undergoing interventional therapy, whether percutaneously or surgically, closure may be necessary if there is a significant left-to-right shunt. This condition is characterized by the

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3 An overview of treatment for atrial septal defect with pulmonary hypertension

7 enlargement of the right heart due to volume overload, regardless of the symptoms (Fraisse, Latchman, Sharma, Bayburt, Amedro, Di Salvo, & Baruteau, 2018). According to Takaya et al.'s 2022 research on the conditions for ASD closure, transcatheter closure is safe if the PAH is mild or appears reversible after shunt closure (Takaya, Akagi, Sakamoto, Kanazawa, Nakazawa, Murakami, Yao, Nanasato, Saji, Hirokami, Fuku, Hosokawa, Tada, Matsumotolmai, Nakagawa, & Ito, 2022).

19 Therapy in patients with intermediate probability of PH

19 The study found that the group with an intermediate probability of PH received supportive therapy and special treatment for PAH, including sildenafil and beraprost, due to a significant increase in PAH (Humbert, Kovacs, Hoe, 20 Badagliacca, Berger, Brida, Carlsen, Coats, Escribano-Subias, Ferrari, Ferreira, Ghofrani, Giannakoulas, Kiely, Mayer, Meszaros, Nagavci, Olsson, Pepke-Zaba, & Sivakumaran, 2022). As per the PH classification based on the mPAP value, this group had an mPAP value of 5-17 mmHg, indicating fluid overload and increased workload of the right ventricle. The right ventricle adapts to the increased vascular load by increasing contractility as per the Frank-Starling law, maintaining RV-arterial coupling and blood flow to peripheral needs (Kazimierczyk, Malek, Szumowski, Nekolla, Blaszczyk, Grzywna, Musial, & Kaminski, 2021). This is the reason for providing supportive therapy and specific therapy to patients with an intermediate probability of pulmonary hypertension (PH) is to prevent more progressive cardiac remodeling which can lead to right heart failure. Specific pulmonary arterial hypertension (PAH) therapy, which works as a pulmonary vasodilator, is added to provide further support. The main objective of this therapy is to prevent the worsening of symptoms and further damage to the heart (Ren et al., 2019).

In this study, it was found that three patients required both surgical and percutaneous ASD closure simultaneously due to device movement or other errors. The study presented by Fraisse et al. also noted this phenomenon and stated that transcatheter closure is generally suitable for such defects, except when there is a deficiency of the

posteroinferior edge towards the inferior vena cava, which can increase the risk of premature device embolization. Even if the device can be installed and positioned well in these cases, the defect can easily enter the inferior vena cava, leading to complications. Generally, device migration occurs immediately or within a few hours after implantation (Fraisse et al., 2018).

16 Therapy in patients with high probability of PH

16 In this study, the results of medical therapy used in ASD patients with a high probability of PH were specific PAH therapy (sildenafil and beraprost) and supportive therapy as previously explained. However, there are several differences that can be seen compared to patients with intermediate probability of PH. In patients with a high probability of PH, the therapy given is more varied and higher doses, such as beraprost, furosemide, and others. Apart from increasing the dose, patients with a high probability of PH also receive a more varied type of therapy, for example administering aspirin and warfarin after ASD closure to prevent thrombus formation after the procedure. This is because patients with a high probability of PH have mPAP values above 70 mmHg, and are at risk of experiencing congestion and right heart failure due to fluid overload (Ren et al., 2019). Therefore, they require more active therapy. It is generally safe to perform transcatheter closure if the patient's pulmonary arterial hypertension (PAH) is mild or appears to be reversible following shunt closure. However, if the PAH is severe, transcatheter closure is not recommended. For this reason, medical therapy is often prioritized for patients with a higher probability of developing PH. The goal is to first control the PAH or reduce the pulmonary vascular resistance (PVR) values so that it can be safely tolerated before proceeding with closure. This is supported by the statement in Takaya et al. research in 2022, that as many as five patients did not undergo shunt closure during treatment with specific PAH drugs because there was no significant reduction in PVR after administering medical therapy (Takaya et al., 2022).

Since the high probability of PH is one of the contraindications for delivering patients with interventional therapy, a thorough evaluation is required, encompassing cardiac catheterization,

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hemodynamic assessment before and following 100% oxygen, inhalation, and balloon occlusion, as well as clinical assessment, electrocardiography, radiography, and echocardiography. to assess the reversibility of pulmonary hypertension while in the defect (Dalvi, Jain, & Pinto, 2019). According to the data obtained, almost 89% of patients with a high probability of PH received percutaneous ASD closure treatment. This is in line with the findings of Faccini and Butera's research, which states that nearly 85-90% of all secundum ASDs can be treated with a transcatheter method (Faccini & Butera, 2018). This is due to the fact that percutaneous ASD closure has various advantages over surgical ASD closure. The avoidance of thoracotomy and cardiac bypass, the decrease in blood product requirements, and the reduction of patient discomfort, morbidity, and post-operative problems are some of these advantages (Putra, Djer, Idris, Samion, & Sastroasmoro, 2015).

Correlation between Patient Probability of PH and provision of interventional therapy

The results of the contingent relation test indicate that the probability of pulmonary hypertension (PH) in a patient does not have a significant impact on whether they are provided with intervention therapy or not. For instance, surgical ASD closure therapy is the preferred choice of treatment only for patients with intermediate PH probability, whereas it should be the primary therapy for those with a high probability of PH, given that a higher mean pulmonary arterial pressure (mPAP) value contraindicates percutaneous ASD closure therapy (Takaya et al., 2022). In addition, the indications and conditions of the patient-such as PAH, which is still reversible after closure, dilatation of the right atrium and ventricle, and the patient's anatomical state of the heart-are taken into focus when delivering interventional therapy (Fraisie et al., 2018). Apart from that, a comparison can be made with a case-control study published in the Bali Medical Journal, which states that patients aged 18 years and below, with a low probability of PH, underwent surgical ASD closure therapy as the main intervention. This was due to the type of ASD experienced by the patients, which was ostium primum ASD and did not allow for percutaneous closure (Rampengan & Rosmaningtyas, 2023). It

cannot be concluded that administering interventional therapy to ASD patients with pulmonary hypertension is solely dependent on the probability level of the patient's PH. One possible reason for this is that the sample size used in the study was too small to establish a significant correlation between PH probability level and intervention therapy.

CONCLUSION

At Prof Ngoerah General Hospital Denpasar, the majority of ASD patients with complications of pulmonary hypertension were females aged between 21 to 30 years. The medical therapy given is adjusted based on the severity of PH as assessed through echocardiography examination. Majority of patients received supportive therapy compared to specific therapy for PAH. Medical therapy is prioritized for patients who have contraindication criteria for interventional therapy. Percutaneous ASD Closure was found to be the largest percentage in interventional therapy regardless of the severity, except for patients who were indicated to undergo surgical ASD closure. There is no significant relationship between the patient's PH probability level and the choice of intervention therapy.

SUGGESTION

Based on the research findings, the author recommends conducting additional longitudinal studies to observe the patient's condition and circumstances over an extended period of time. This can help provide a better understanding of the patient's needs and inform the development of effective therapies. In addition, it may be helpful to gather more detailed data beyond medical records.

RESEARCH LIMITATIONS

There are certain limitations in conducting this research. These limitations arise due to the fact that the data used in this research is taken from secondary sources such as medical records, which may not guarantee complete recording of all relevant information. Additionally, some crucial data required to determine the best therapy for a patient is not always recorded in the medical records, such as the type of ASD suffered by the patient and the PVR value, which is a critical criterion for providing intervention therapy to patients. In such cases, the

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therapy data is obtained without considering the criteria or characteristics used for providing therapy. Furthermore, the sample size used in this study is still too small to be used in analytical calculations of correlation tests between the probability level of a patient's PH and the intervention therapy given.

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