Outcomes in Pulmonary Hypertension Among Adults Undergoing Percutaneous Atrial Septal Defect Closure

By

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A dissertation submitted in conformity with the requirements for the degree of Master of Science in Health Service Research
Institute of Health Policy, Management and Evaluation
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Executive Summary

Atrial septal defects (ASDs) are one of the most common forms of congenital cardiac lesions diagnosed during adulthood. If left untreated, ASDs can lead to right ventricular failure and pulmonary hypertension (PH). Patients with PH and ASD suffer from worse prognoses than patients without PH. The role of ASD closure and its effects on PH remain unclear and information regarding the relationship between ASD closure and PH is limited. The first objective of this thesis was to synthesize the current body of ASD with PH literature through a systematic review and meta-analyses. Our second objective was to produce a high-quality cohort study assessing long-term outcomes of ASD closure between patients with and without PH. We found that PH prevalence and mean pulmonary arterial pressure decrease after ASD closure. Our analyses found that ASD patients with PH undergoing closure experience more comorbidities and worse long-term outcomes, compared to patients without PH.

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This thesis is dedicated to my parents, Dr. Mir Ahmad Akseer Shinwari, and Ambara Akseer. Your sacrifices are the inspiration behind every life milestone. Your love is the fuel to success, and your guidance is the roadmap. Thank you, Lala and Babai for helping me stand yesterday, today and tomorrow.

Above all, I acknowledge it is my faith that drives my ambition and motivation to learn. Words remain insufficient to describe my gratefulness and appreciation to God. I thank God for all the

opportunities, challenges, and strength that have guided me from my early education to today. May He continue to bless, inspire and motivate me while I navigate this journey.

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List of abbreviations

ACC: American College of Cardiology

ACE: angiotensin-converting enzyme

AF: atrial fibrillation

AHA: American Heart Association

AMI: acute myocardial infarction

ASD: atrial septal defect

BMI: body mass index

CAD: coronary artery disease

CCI: Charlson comorbidity index

CHD: congenital heart disease

CI: confidence interval

CIHI: Canadian Institute for Health Information

COPD: chronic obstructive pulmonary disease

CV: cardiovascular

DAD: Discharge Abstract Database

ED: emergency department

ERS: European Respiratory Society

ESC: European Society of Cardiology

HF: heart failure

HR: hazard ratio

ICD: International Classification of Disease

ICES: Institute for Clinical Evaluative Sciences

IKN: Institute for Clinical Evaluative Sciences key number

IQR: interquartile range

JBI: Joanna Briggs Institute

LV: left ventricle

LVEDD: left ventricle end-diastolic diameter

LVEDP: left ventricular end-diastolic pressure

LVFP: left ventricular filling pressure

MACCE: major adverse cardiac and cerebrovascular events

MI: prior myocardial infarction

mPAP: mean pulmonary arterial pressure

MRI: magnetic resonance imaging

NA: not applicable

NR: not reported

NYHA: New York Heart Association

OHIP: Ontario Health Insurance Program

PAH: pulmonary arterial hypertension

PAP: pulmonary arterial pressure

PCWP: pulmonary capillary wedge pressure

PH: pulmonary hypertension

PHM: pulmonary hypertension medication

PMCC: Peter Munk Cardiac Centre

PPI: permanent pacemaker implantation

PRISMA: Preferred Reporting Items for Systematic reviews and Meta Analyses

PVD: pulmonary vascular disease

PVR: pulmonary vascular resistance

PY: person years

Qp:Qs: pulmonary to systemic flow ratio

RAD: right atrium diastolic

RHC: right heart catheterization

RV: right ventricular

RVEDD: right ventricle end-diastolic diameter

RVMPI: right ventricle myocardial performance index

RVSP: right ventricular systolic function

SD: standard deviation

SMD: standardized mean difference

sPAP: systolic pulmonary arterial pressure

TAPSE: tricuspid annular plane systolic excursion

TEE: transesophageal echocardiogram

TGH: Toronto General Hospital

TR: tricuspid valve regurgitation

TTE: transthoracic echocardiogram

UHN: University Health Network

WSPH: World Symposium of Pulmonary Hypertension

WU: Wood Units

Chapter 1. Introduction

1.1 Pulmonary hypertension

1.1.1 Definition and evaluation method

Pulmonary hypertension (PH) is a disorder that can develop as a complication of several cardiovascular and respiratory lesions. PH is characterized by vasoconstriction and the remodelling of pulmonary arteries. PH has been defined as a sustained elevation of mean pulmonary arterial pressure (mPAP) equal to or greater than 25 mmHg at rest, as measured during right heart catheterization (RHC) (1). Pulmonary arterial pressures (PAPs) are usually measured by RHC, an invasive procedure that enables direct hemodynamic measurements of the right heart and pulmonary vessels (2). During RHC, a thin catheter (long hollow tube) is inserted into a vein (e.g. femoral or jugular) and guided towards the right ventricle to measure systolic and diastolic pressures, mPAP and cardiac output. Since the 1st World Symposium on Pulmonary Hypertension (WSPH) in 1973, PH has been defined as a presence of an mPAP ≥ 25 mm Hg at rest, measured by RHC (3). The clinical significance of an mPAP between 21 and 24 mmHg, often referred to as borderline PH, remains unclear; patients with borderline PH experience increased morbidity and mortality compared to those with lower mPAP and are considered an at-risk subgroup (4-6). Recently, at the 2019 6th WSPH meeting, experts applied a scientific approach to mPAP measurement and proposed a lowering of the mPAP cut off from ≥ 25 mm Hg to > 20 mm Hg as a diagnostic cut-off (6). This change came from applying the rules of the normal distribution to data showing that healthy patients have a normal mPAP equal to 14.0 ± 3.3 mmHg (7). Two standard deviations above this mean value equals to an mPAP of 20.6 mmHg, or the upper limit of a normal mPAP. Values above this (i.e., above the 97.5th percentile) are outside of the normal mPAP range and, therefore, fulfill the clinical requirements of PH diagnoses. While the new cut off is not reflected in the current clinical guidelines, it is expected to be considered in the new guidelines moving forward (6).

1.1.2 Classification

Historically, pulmonary hypertension has been classified as either primary or secondary (8). The World Health Organization (WHO) has established a clinical classification system to differentiate PH into categories which share similar pathology, hemodynamics, and management modalities (Table 1). The five subgroups of disorders include: *Group 1*, pulmonary arterial

hypertension (PAH); *Group 2*, pulmonary hypertension due to left heart disease; *Group 3,* pulmonary hypertension due to chronic lung disease and/or hypoxia; *Group 4*, chronic thromboembolic pulmonary hypertension; and *Group 5*, pulmonary hypertension due to unclear multifactorial mechanisms (9). The term pulmonary hypertension is used to describe all five subgroups of PH. Pulmonary arterial hypertension (PAH) is used to describe Group 1 PH. A diagnosis of PAH includes low wedge pressure (PAWP) of $\leqslant$ 15 mmHg and a high pulmonary vascular resistance (PVR) of $\geq$ 3 Woods units. PH can occur as a complication among patients with congenital heart disease (CHD). It is important to distinguish between different clinical scenarios that may be encountered in PH and ASD. PH may occur with age in significant ASDs; this is usually a modest to moderate increase in mPAP. PAH is unrelated to defect size, and generally more severe. Presence of PAH likely suggests an underlying secondary pulmonary vascular disorder (10, 11).

Table 1. Clinical classifications of pulmonary hypertension (12)

WHO class	**Subgroups**	**Distinguishing features**
Group 1	1. Pulmonary arterial hypertension 1.1. Idiopathic PAH 1.2. Heritable PAH 1.3. Drugs and toxin induced PAH 1.4. Associated with: 1.4.1. Connective tissue disease 1.4.2. Human immunodeficiency virus 1.4.3. Portal hypertension 1.4.4. Congenital heart disease 1.4.5. Schistosomiasis 1.5. PAH long-term responders to calcium channel blockers 1.6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement 1.7. Persistent PH of the newborn	Presence of pre-capillary PH and pulmonary vascular resistance (>3 Wood units) in the absence of other causes of pre-capillary PH (such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases)
Group 2	2. PH due to left heart disease 2.1. PH due to heart failure with preserved LVEF 2.2. PH due to heart failure with reduced LVEF 2.3. Valvular heart disease 2.4. Congenital/acquired cardiovascular conditions leading to post-capillary PH	PH due to left heart disease
Group 3	3. PH due to lung diseases and/or hypoxia 3.1. Obstructive lung disease 3.2. Restrictive lung disease 3.3. Other lung disease with mixed restrictive/obstructive pattern	PH due to chronic lung disease and/or hypoxia

	3.4. Hypoxia without lung disease 3.5. Developmental lung disorders	
Group 4	4. PH due to pulmonary artery obstructions 4.1. Chronic thromboembolic PH 4.2. Other pulmonary artery obstructions	PH due to pulmonary artery obstructions
Group 5	5. PH with unclear and/or multifactorial mechanisms 5.1. Haematological disorders 5.2. Systemic and metabolic disorders 5.3. Others 5.4. Complex congenital heart disease	PH due to unclear multifactorial mechanisms

1.1.3 Pulmonary arterial hypertension associated with adult congenital heart disease

High pulmonary arterial pressure reduces blood flow to the lungs and causes low cardiac output. In patients with shunts, this can cause deoxygenated blood to move into the systemic circulation. Advancements in CHD management have led to an increase in survival of CHD patients into adulthood. These improvements, combined with advancements in therapies and technology, could be the drivers of the increase in adult CHD prevalence observed in recent decades. Currently it is estimated that 10% of adults with PAH have CHD (13). PAH associated with CHD typically follows one of four clinical scenarios (Table 2).

Table 2. Clinical classification of pulmonary arterial hypertension associated with congenital heart disease (12)

1. Eisenmenger syndrome	Includes all large intra- and extra-cardiac defects. These can begin as systemic-to-pulmonary shunts, with time they progress to severe elevation of pulmonary vascular resistance (PVR) and to reversal shunting or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are typically present.
2. PAH associated with systemic-to-pulmonary shunts	Can be correctable or non-correctable; includes moderate to large defects; PVR can be mildly to moderately increased, left to right shunting is still prevalent, and cyanosis is not a feature.
3. PAH with small defect	Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease; marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Defect closure is contraindicated.
4. PAH after defect correction surgery	Congenital heart disease is repaired but PAH may either persist immediately after surgery or develops months or years after

	surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

1.2 Secundum atrial septal defect

1.2.1 Definition and anatomy

Atrial septal defects (ASDs) are one of the most frequent congenital cardiac malformations. They are characterized by an opening in the interatrial septum. Blood typically travels through an opening from left to right because the left atrium has a higher pressure than the right atrium. Increased flow to the right heart causes dilation of the right atrium and right ventricle leading to a chronic state of volume overload. The magnitude of interatrial blood exchange is determined by the size of the defect and difference in compliance between the two atrial chambers.

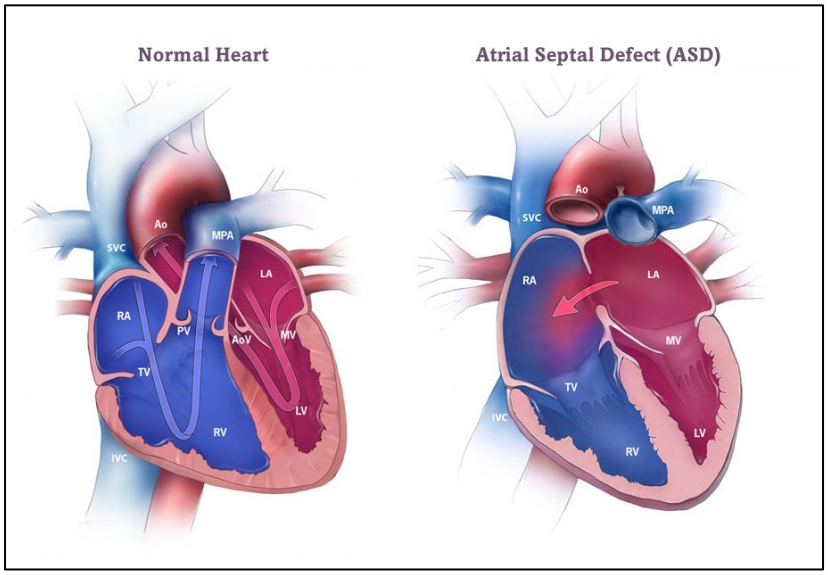

Figure 1 https://www.achaheart.org/your-heart/health-information/atrial-septal-defect/

1.2.2 Classifications and prevalence

CHD accounts for nearly one third of all birth anomalies globally (14). ASDs are the most common form of adult CHD lesion, accounting for 75% to 90% of observed cases (15). The estimated Canadian prevalence of ASDs is 84 per 100 000 adults (16). There are 4 types of ASD secundum ASD, sinus venous ASD, ostium primum ASD, and coronary sinus ASD (Table 3). Ostium secundum is the most predominant form, typically occurring in the mid atrial septum, in

the fossa ovalis, and accounts for 75% to 90% of all ASDs (17, 18). Secundum ASD has a female predominance of about 2:1 (19).

Table 3. Clinical classification of ASD lesions (17, 20)

	Distinguishing features	Defect location	Proportion of observed ASD cases (13)	Male: female ratio	Recommended Therapy (21)
Ostium Secundum ASD	Left to right shunts in atrial septum leading to right ventricular overload	Fossa ovalis	91%	2:1	Percutaneous closure
Sinus venous defect	Associated with partial anomalous pulmonary venous return (90%)	Posterior wall of vena cava	7%	1:1	Surgical repair/transcatheter techniques
Ostium primum	Atrioventricular septal defect	Atrial ventricular septum	2%	1:1	Surgical repair
Coronary sinus	Rare unroofing of the coronary sinus to the left atrium	Left atrium	<1%	1:1	Surgical repair/transcatheter techniques

1.2.3 Pathophysiology

ASDs create a connection between systemic and pulmonary circulations. Physiological changes that occur are dependent on the magnitude and direction of blood flow through the shunt and are driven by the size of the defect and relative compliance of the chambers on either side. Under normal conditions, right ventricular compliance is higher, resulting in more left to right flow though the ASD (22). A left to right shunt can cause right ventricular volume overload and the recirculation of oxygenated pulmonary blood through pulmonary vasculature. Right ventricular volume overload enlarges the right ventricle and atrium and impairs left ventricular diastolic function (23). The redirection of left atrial flow through an ASD into the right side of the heart can lead to a reduction in the systemic cardiac output (23).

The extent of interatrial communication is assessed using the Qp:Qs ratio, where the Qp is the measured pulmonary blood flow and Qs is systemic blood flow. In a healthy patient where no

communication between atria exists, the Qp:Qs ratio is 1:1. In typical secundum ASDs where there is a significant left to right shunting the Qp:Qs is>1, an indication that the pulmonary flow is greater than the systemic flow (23). Typically, an ASD greater than 10 mm in diameter can cause a significant left to right shunting and a Qp:Qs ratio greater than 1.5. The defect size is a determinant of the resistance to flow, with larger defects allowing more blood to pass through and smaller more restrictive defects limiting the blood flow (24). Smaller defects do not typically result in significant right ventricular volume overload.

1.2.4 Natural history

The natural history of an ASD depends on the size of the defect, right and left ventricular diastolic compliance, and pulmonary to systemic vascular resistance. Hemodynamic and structural abnormalities resulting from an ASD include right ventricular and atrial volume overload, pulmonary vascular obstructive disease, tricuspid and/or pulmonary valve regurgitation, and supraventricular tachyarrhythmias. ASD shunt direction and magnitude are variable and largely age dependant. Most infants with an ASD are asymptomatic (25).

Immediately following the birth, RV compliance is similar to the LV and there is a little net shunting through the ASD; the timing of the clinical presentation of an ASD depends largely on the degree of shunting. A study comparing six infants with failure to thrive that underwent ASD closure, found that five infants had other significant cardiopulmonary disorders attributing to the cause of their failure to thrive (25). During a physiological fall in pulmonary vascular resistance the RV compliance increases, and a left-to-right shunt develops. Although secundum ASDs are congenital defects, they may be detected from childhood until late adulthood. Most children and adolescents with an ASD generally remain asymptomatic, with symptoms typically increasing or appearing progressively with age. With each decade, patients may recognize a subtle deterioration in function; however, it is often attributed to poor physical conditioning, weight gain, or age. Patients with smaller ASDs (i.e. less than 5mm) may not develop symptoms, whereas patients with larger ASDs (i.e. greater than 5mm) may present with symptoms in their fourth or fifth decade of life (26).

An early study on the natural history of ASDs reported increased mortality with age. Campbell reported the first and second decades of life with an ASD were shown to have an all-cause mortality rate of 0.7 and 0.6% per year, respectively (27). All-cause mortality rates during the third and fourth decades increase from 2.7 to 4.5%, respectively (27). Campbell's work from 1970 is the only study reporting the natural history and all-cause mortality of ASDs. This paper predates modern day ASD diagnostic tools and likely reports results from a more severe ASD population. This affects the generalizability to the current population of patients undergoing ASD closure, these mortality rates may not be clinically relevant. A recent review of 479 ASD closure patients under the age of 40 found the most common preoperative symptoms were dyspnea and increased fatigue (28). Other symptoms include RA and RV dilation, tricuspid regurgitation, and atrial arrythmias. Just 4% of ASD patients over the age of 40 experienced no symptoms (29). There are other contributing factors (e.g. shunt size, patient characteristics) that contribute to the demonstrated increase in mortality in patients with an ASD. In an effort to confirm dimensions related to an ASD, there are several diagnostic modalities that can be employed, namely, echocardiography and catheterization.

1.2.5 Diagnostic methods

Echocardiography

Echocardiography is the screening tool of choice when evaluating the presence of an ASD. It is a non-invasive diagnostic tool used in cardiac structure and functional imaging in real time. Echocardiographic evaluation of an ASD provides an accurate means to detect and quantify the defect size, the degree and direction of shunting, and the remodeling and changes in size and function of the cardiac chambers and pulmonary circulation. There are two types of echocardiograms used; transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). The most widely used ultrasound modality to evaluate the interatrial septum and detect an ASD is TTE (30-32). TTE allows for the estimation of the right atrium, right ventricle, and estimation of the shunt ratio from the Doppler velocity of tricuspid regurgitation. While TTE can be used as an initial diagnostic tool for ASD, its image quality may not always permit comprehensive evaluation of the interatrial septum, therefore, further characterization using TEE may be useful. TEE provides further characterization of atrial septal abnormalities and describe the pulmonary venous return. Some studies suggest TEE be

performed in all adult patients that are undergoing percutaneous ASD closure (33-35). TEE provides clearer images of cardiac structures that are typically more difficult to view with transthoracic images because the esophageal wall is closer to the heart. It is commonly used for guidance during percutaneous ASD closure. Overall, echocardiography in patients undergoing percutaneous ASD closure is important for appropriate selection of eligible patients, intraoperative use, post-operative assessment of closure device efficacy, and long-term patient follow up (Table 4).

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) imaging is another measurement modality for non-invasive imaging of ASDs. It can determine ASD location, size, shunt flow, and direct flow measurements with a high degree of accuracy. CMR agrees closely with TEE assessments of ASDs for percutaneous closure (36). CMR can quantify left to right shunting metrics similar to invasive cardiac catheterization, with values reflecting a high degree of agreeability and a clinically insignificant overestimation of flow (37). Despite being the most accurate non-invasive imaging tool, CMR is less than ideal with its associative high costs and limited availability.

Right heart catheterization

Right heart catheterization (RHC) is an invasive test used to confirm the presence of a hemodynamically significant shunt as well as provide accurate measurements of atrial and ventricular pressures within the heart. A catheter is inserted into a vein and guided towards the right side of the heart. Measures such as cardiac output (CO), shunt size (Qp:Qs), systolic pulmonary arterial pressure (sPAP), mean pulmonary arterial pressure (mPAP), pulmonary artery diastolic pressure, pulmonary arterial wedge pressure (PAWP), ventricular pressures, and pulmonary vascular resistance (PVR) are recorded. RHC is usually performed after non-invasive tests have suggested an ASD with or without pulmonary hypertension. RHC is also used to further classify PH into pre-capillary or post-capillary groups based on PAWP. PAH is determined by a PAWP $\leqslant$15 mmHg in addition to a mean PAP $\geq$ 25 mmHg at rest and a pulmonary vascular resistance (PVR) > 3 Wood units (38).
(39)

Table 4. Advantages and disadvantages of ASD measurement modalities (39)

		Advantages	Disadvantages
Non-invasive	TTE	Primary screening tool	Poor accuracy; interoperator variability in imaging; limited to frontal cardiac structures; 89% sensitivity compared to RHC (40)
	TEE	Better resolution than TTE; provides posterior cardiac images; high sensitivity in ASD diagnosis; preferred method of diagnosis over TTE	Interoperator variability in imaging; requires expert imager
	CMR	Accurate 3D imaging	Expensive; less available than echo
Invasive	RHC	Accurate assessment of hemodynamics; can be used to guide ASD procedure	Expensive; vascular access site complications (rare)

CMR, cardiac magnetic resonance; RHC, right heart catherization; TEE-transesophageal echocardiography; TTE, transthoracic echocardiography.

1.2.6 Treatment methods for ASD

For many years, open-heart surgical closure, using median sternotomy and cardiopulmonary bypass, were the gold standard treatment option for ASD repair. The surgical technique for repairing uncomplicated ASDs involves a direct suture repair, by longitudinal or transverse opening of the right atrium. Larger defects typically require an autologous or synthetic pericardial patch to cover and close the ASD (41). Since the first report of ASD surgical repair in 1952, many years of surgical repair procedures have led to its minimal morbidity and mortality rates among patients. Surgical ASD closure has been shown to be a safe procedure with a low risk of mortality among patients. Studies assessing long term patient follow up have outlined the safety and efficacy of surgical repair (42-44). Survival curves following surgical repair are shown the be identical to the general healthy population when the patient receives treatment before the age of 25 (43). Older patients undergoing surgical repair also experience increased long-term morbidity and mortality (45, 46).

Although surgical closure was once considered the standard treatment option, following advancements in cardiac surgical methods and evolution of surgical techniques, percutaneous device closure is now the preferred therapeutic approach (47, 48). In 1976, King and colleagues were the first to report successful percutaneous closure of an atrial septal defect using a double disc device implanted through a transvenous sheath (49). Percutaneous device closure can be

performed as an outpatient procedure with local anesthesia. In this method, a self-expandable round device is selected and placed around the left-to-right shunt. Typically, the device size is 1–2 mm larger than the width of the ASD. Since 1997, the most commonly used device for percutaneous ASD closure is the Amplatzer Septal Occluder (50, 51). Other devices include the Gore Cardioform ASD occlude and the Figulla Flexible II Occluder.

Studies comparing the efficacy and safety of percutaneous closure with surgical closure have found them both to be safe and effective treatment options with similar long term outcomes among patients (48, 52). A systematic review and meta-analyses comparing surgical closure versus percutaneous closure of ASDs found that percutaneous treatment had a significantly lower rate of either total or major early postprocedural complications when compared to traditional surgical methods (53). The main advantages of percutaneous closure are the high defect sealing rates (between 97% to 99%), shorter procedure times and length of hospital stay, avoidance of cardiopulmonary bypass and associated sternotomy scar, less discomfort for the patient, and lower cost (48, 54). Percutaneous closure is also less invasive and avoids problems typically encountered in open heart surgery (i.e. anesthesia, cardiopulmonary bypass, thoracotomy, etc.). Major complications occur among approximately in 0.01% to 0.1% of patients and include device embolization, cardiac erosions, new onset atrial arrhythmia, atrioventricular block, and thromboembolism (55).

The 2018 American Heart Association guidelines for the management of adults with CHD, state the following indications for percutaneous closure: hemodynamically significant secundum type ASD causing impaired functional capacity, right atrial and/or right ventricular enlargement, and a net left-to-right shunt sufficiently large (i.e. Qp:Qs ratio ≥ 1.5:1) without cyanosis at rest or during exercise (56). Contraindications to percutaneous closure include: small secundum ASD with no hemodynamic significance, ASDs other than those of the secundum type (including primum type, sinus venosus type, and unroofed coronary sinus defects), and secundum ASD with advanced pulmonary hypertension (56). Among patients with ASD types other than secundum, surgical repair may be considered. In patients who have a small ASD that is not hemodynamically significant, the ASD could be a bystander and does not require intervention. Guidelines state that patients undergoing percutaneous closure of their secundum ASD with a

diagnosis of pulmonary hypertension require special consideration and care (56). This is discussed in greater detail in Section 1.3.3.

1.3 Pulmonary hypertension in adults with ASD

1.3.1 Prevalence of PH among patients with ASD

Patients with ASDs can develop PH, a chronic condition characterized by a progressive increase in RV pressure and pulmonary vascular resistance (PVR). Increased right sided cardiac output leads to an increase in pulmonary circulation and pulmonary pressure. The result is remodelling of the pulmonary vasculature which includes increases in pulmonary vascular resistance, pulmonary wedge pressure, and a condition known as pulmonary arterial hypertension. PH is an important complication in patients with hemodynamically significant ASDs, as it negatively affects outcomes (1). The estimated prevalence of PH among ASD patients has been reported to be between 10% (8) – 20% (19, 57, 58). Reports on prevalence estimates are highly variable and susceptible to over or underestimation depending on case definitions and measurement modalities used. Generally, the severity of PH should decrease following ASD closure (59).

1.3.2 Diagnosis and assessment of PH among patients with ASD

While electrocardiography and non-invasive imaging may suggest the presence of ASDs, their sensitivity in correctly detecting cases of pulmonary hypertension is low (60, 61). Despite its utility in diagnosing ASDs, echocardiography provides limited information on the state of the pulmonary vasculature.

Right heart catheterization (RHC) is the gold standard diagnostic test for a definitive diagnosis of pulmonary hypertension (38). RHC must be used to definitively classify PH subgroups by measuring pre-capillary and post-capillary PH pressures based on their pulmonary arterial wedge pressures (PAWP) and pulmonary vascular resistance (PVR). The use of RHC is imperative in distinguishing PAH due to CHD as it also provides haemodynamic parameters needed to assess cardiac impairment and characteristics related to the ASD. An updated diagnostic algorithm highlighting the central role of RHC in the diagnosis of PAH has been posted by The European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines (1). RHC is the gold standard for diagnosing PH at some, but not all centres, in the routine diagnostic work up of

ASD (62). This can be because of the perception of increase risks due to its invasive nature when compared to echocardiograms, as well as its associated costs. The ability of RHC to accurately measure PAP and PAWP allows operators to determine shunt size and pulmonary blood flow and calculate PVR. PVR is calculated by dividing the pressure gradient across the lungs by the pulmonary blood flow. PVR can be calculated by subtracting the mean pulmonary capillary wedge pressure from mPAP, divided by the cardiac output and multiplied by 80 (63). PVR is an important prognostic measure when evaluating the state of the vascular bed before and after any procedure (63).

Sources of error

RHC measurement among ASD patients with PH is prone to errors unless care is taken in the procedural approach. There has been documentation of interoperator differences relating to the positioning of pressure measures and therefore hemodynamic readings between care centres (38). Standardization of the procedure is necessary to ensure reliable, accurate, and comparable hemodynamic data among and across patients. When estimating PAWP during RHC, the catheter tip inserts an inflated balloon into a small pulmonary artery. PAWP uses expiratory effort to measure the left ventricular end-diastolic pressure (LVEDP), which is a proxy in determining left ventricular filling pressure (LVFP). The measurement of pulmonary arterial wedge pressure itself is vulnerable to over or under wedging, leading to false readings. Studies have found that PAWP frequently underestimates LVEDP and preforms poorer than LVEDP when differentiating between PH subgroups (64, 65). Another study found that roughly half of the PAH diagnoses made by PAWP were actually pulmonary venous hypertension when assessed by LVEDP (65). Interpretation of PAWP readings and subsequent PH subgrouping should be approached with caution.

Another source of error and drawback of haemodynamic evaluation is determining the blood flow among patients. Current methods used to quantify cardiac output and the degree of shunting are based on the Fick principle; the underlying idea is that the total oxygen consumption by peripheral tissues or cardiac output, can be calculated by dividing the oxygen consumption over the difference in oxygen content between pulmonary arteries and the veins (66). To accurately estimate pulmonary blood flow, repeated sampling of patient oxygen saturations is

recommended. Alternatively, the right atrial pressure can also be used as a prognostic measure in detecting PH among patients with ASD. Typically, the right atrial function is impaired among patients with PH compared to healthy controls (67).

1.3.3 Treatment approaches for ASD and PH

Patients with ASDs in the presence of PH can be repaired surgically or by percutaneous closure. Over the past 25 years, major advances have been made in percutaneous interventions in the treatment of ASDs (68), making it the recommended standard of care for patients with PH and ASDs. The lower complication rate, shorter length of stay, more rapid recovery, more rapid return of cardiac function and reduced scare formation make percutaneous closure a more attractive option for patients as well (48, 53). ASD closure considerations change depending on the clinical scenario of PH.

ASD with post capillary PH

An ASD with post capillary PH is typically associated with elevated LVEDP. This is more common among aging populations, when the shunt volume through an ASD is increased due to a rise in left heart filling pressures. This scenario is likely to be secondary to the development of age-related conditions such as hypertension and ischemic heart disease; elderly patients can also have other risk factors such as diabetes, atrial fibrillation, and chronic kidney disease. Because of these conditions, even anatomically "small" shunts can lead to significant pulmonary to systemic flow leading to RV overload (69). A study by Jategoankar and colleagues reported that even an ASD of 1cm in diameter can be hemodynamically significant in elderly patients with PH (70).

ASD associated with PH

ASDs associated with PH can follow the different clinical scenarios outlined in Table 2. The first includes adults with and without pulmonary vascular disease and a large shunt; these patients should undergo a percutaneous closure (12). Patients with Eisenmenger etiology, that is, a large defect with severe irreversible PVD, should be managed medically (12). Patients with PH and a small ASD (e.g., < 2cm and not hemodynamically significant), have a clinical picture similar to idiopathic PH, and the relevance of the defect to the development of PH is unclear (11). In this scenario the defect is likely a bystander and has no pathophysiologic effect on causing PH to

occur. These patients should be treated for their PH medically with vasodilators, as a closure of their ASD is not required (11). Finally, the most difficult subset of patients to treat are those with severe PH and a relatively large left to right ASD. There are no specific guidelines for ASD closure in the presence of severe PH. These patients should be treated on a case by case basis to determine if the patient will benefit from an intervention (56). The *Treat and Repair Strategy* method has been shown to help manage PH until patients are in an acceptable PVR range to have ASD surgery. In this method, patients with large atrial septal defects and severe PH are pretreated with pulmonary vasodilators, typically 3 months prior to ASD closure (71). PH specific medications include endothelin-receptor antagonists, phosphodiesterase type-5 inhibitors and oral and intravenous prostanoids. If the patient responds well to PH medications, then transcatheter closure of the ASD may be performed with or without device fenestration. This method has been shown to provide improvement in immediate and short-term outcomes (i.e hemodynamics and clinical parameters) (72, 73). However, there is a lack of information on the long term effects of the *Treat and Repair Strategy*; larger studies with long term follow up are needed to evaluate it effects (74).

1.3.4 Current guidelines and recommendations for ASD treatment

The ESC/ERS guidelines (1) and the more recent American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Adults with Congenital Heart Disease (56) outline indications for ASD closure among patients with PH (Table 5). The ESC/ERS guidelines state that moderate to large defects associated with left to right shunting should be corrected when PVR index (PVRi) is < 4 Wood units/m^2 (WU·m^2). When PVRi values are between 4-8 WU·m^2, a PH expert consultation in specialized centers is recommended to make decisions on a case by case basis. A PVRi of > 8 WU·m^2 is a contraindication to closure due to increased operative risks. The 2018 ACC/AHA guidelines indicate closure of ASDs in a variety of clinical scenarios. The first indication for closure includes impaired functional capacity (based on the WHO functional capacity scale), right atrial or ventricular enlargement, and a net pulmonary to systemic flow with a Qp:Qs ratio ≥ 1.5:1 (56). Closure is recommended among patients with sPAP less than 50% of systemic pressure combined with PVR of one third systemic vascular resistance or less. The guidelines state ASD closure can be considered with a

combination of the above conditions. However, ASD closure should not be performed among patients with sPAP > two thirds systemic, and/or a right to left shunt (56).

Table 5. Recommendations for closure of shunt defects among patients with PH

	ESC/ERS guidelines (1)	**AHA/ACC guidelines (56)**	**Canadian Cardiovascular Society (75)**
Yes	PVRi < 4 WU·m^2	sPAP < one half systemic Qp:Qs > 1.5:1	Qp:Qs ≥ 1.5:1 Evidence of Pulmonary artery reactivity
No	PVRi > 8 WU·m^2	sPAP > two thirds systemic Qp:Qs < 1.0	sPAP > two thirds systemic Qp:Qs < 1.0 Irreversible PAH

*Values in between should be considered on a case by case basis by PH and ASD specialists

Current recommendations are tailored towards patients with smaller left-to-right shunts and otherwise normal ASD clinical scenarios. The ESC/ERS guidelines recommend adults with PH and PVRi between 5-8 WU·m^2 consult with a specialist and have their eligibility for closure discussed on a case-by-case basis (1). There is a growing evidence on combined treatment with PH medications prior to ASD closure to decrease PVRi to an acceptable range that will allow for shunt closure (71). Additionally, there are considerably fewer recommendations for patients with PH and moderate to large left-to-right shunts. These complex ASDs with PH are considered to be "borderline inoperable" and clinical treatment decisions are made on a case by case basis (76).

1.4.4 Immediate and long-term outcomes following percutaneous ASD closure

Immediately following percutaneous ASD closure, patients can expect a decline in New York Heart Association (NYHA) functional class (71, 77-88). NYHA functional class is based on patient's severity of symptoms and places patients in one of four categories based on how limited they are during physical activities. NYHA class is a commonly used method for functional classification in the cardiology literature. NYHA class limitations however include interoperater bias, subjectivity and poor reproducibility (89). PH prevalence is thought to decline following ASD closure. Five percutaneous ASD closure cohort studies reported that the PH prevalence decreased after closure (77, 81, 82, 84, 87, 90). In these studies, the prevalence of PH varied from 24% to 62% before closure and to 5% to 31% after closure. Twelve cohorts of ASD patients undergoing percutaneous closure have reported a decrease in the mean systolic pulmonary arterial pressure (sPAP) following ASD closure (78-80, 84-86, 90, 91). sPAP, like

mPAP, can be used in the measurement of PH among patients with ASD with an sPAP > 40 mm Hg cut-off used to define PH (1).

Studies reporting long term outcomes achieved by patients with PH that have undergone percutaneous ASD closure are limited. Further, patient follow up and outcomes reported are widely variable. Most studies report an immediate decrease in PAP and some decrease in PVR following ASD closure (81, 83). Currently there are no long-term follow-up studies that directly compare outcomes between patients with and without pulmonary hypertension undergoing ASD closure. More studies are needed to observe the effect of change in PH on outcomes.

Developing PH after ASD closure

There is a subset of patients that develop PH or have a persistent PH after an ASD repair (10, 92). This can be a result of a post-operative residual shunting, or chronic PH. PH with repaired ASDs has a worse prognosis than PH with unrepaired ASD (1). The immediate development of PH following ASD repair has been hypothesized to occur as a reaction to the loss of decompression of the left atrium from the defect closure revealing left-sided diastolic dysfunction (92). If PH development occurred years after the closure, it could be unrelated to ASD closure and due to increasing age and comorbidities. It has been argued that PH development is an age dependent phenomenon (92). Studies with long-term follow up of patients after ASD closure (with and without PH) and longitudinal measured of reliable and valid hemodynamic data are lacking to comprehensively describe this phenomenon.

1.5 Rationale and aim

ASDs are the second most common form of adult congenital heart defects. A proportion of patients with significant systemic-to-pulmonary shunts will develop PH. PH related to an ASD is associated with increased morbidity including poorer procedural and long-term outcomes leading to poor survival of this patient population. Closure of an ASD in the presence of hemodynamically relevant shunts that lead to right sided chamber enlargement and reduced functional capacity is indicated and shown to be beneficial (93). Percutaneous closure of an ASD has become the gold standard treatment choice as it provides a minimally invasive means to

defect remodeling, as well as reduced morbidity and mortality (57). Evidence regarding the effect of ASD closure on outcomes in patients with PH is highly limited. There are increased risks associated with percutaneous closure of an ASD in patients with a diagnosis of PH and therefore, intervention in this patient population requires special consideration. Long-term follow up studies that evaluate the effect of PH on outcomes are needed, as the current knowledge base is limited. The present thesis project aims to address this knowledge gap by describing characteristics of ASD patients with PH who undergo percutaneous closure and compare their short and long-term outcomes with patients without PH.

1.6 Specific objectives

The two specific objectives address by this thesis include:

1. To describe currently used PH definitions, evaluate the prevalence of PH and the effect of PH on outcomes in ASD patients undergoing percutaneous closure (Chapter 2);
2. To compare clinical characteristics, procedural and long-term outcomes between patients with and without PH, using a clinical registry linked to population-based administrative databases in Ontario (Chapter 3).

Chapter 2. Systematic Review and Meta-Analyses

2.1 Prevalence and Outcomes of Pulmonary Hypertension After Percutaneous Closure of Atrial Septal Defect: A Systematic Review and Meta-Analysis

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2.1.1 Abstract

Background: Atrial septal defect (ASD) is a common form of congenital heart disease. Significant shunts may increase the risk of developing pulmonary hypertension (PH). We aimed to describe current PH definitions, evaluate PH prevalence and the effect of PH on outcomes in patients undergoing percutaneous ASD closure.

Methods: EMBASE, MEDLINE, and Cochrane databases were systematically searched. Studies reporting PH prevalence or mean systolic pulmonary arterial pressure (sPAP) before and after percutaneous ASD closure in adults were included. We conducted meta-analyses to obtain summary estimates for PH prevalence and mean sPAP.

Results: Fifteen articles with a total of 1,073 patients met the eligibility criteria. Studies applied variable PH definitions. PH prevalence and mean sPAP levels decreased in all studies after closure. The pooled PH prevalence decreased from 44% (95% Confidence interval (CI): 29% to 60%) to 18% (95%CI: 8% to 27%). The overall standardized mean difference (SMD) in sPAP was 1.12 (95%CI: 0.81 to 1.44) and 1.62 (95%CI: 1.00 to 2.23) in cohort and case series studies respectively indicating a large decrease. The pooled SMD among the younger and older patients were different, 1.25 (95%CI: 0.78 to 1.71) and 0.91 (95%CI: 0.56 to 1.27) respectively. A high degree of between study heterogeneity was noted.

Conclusions: Both PH prevalence and mean sPAP decrease after ASD closure. Larger, prospective studies with consistent PH definitions using the recommended measurement modality are warranted.

Keywords: atrial septal defect; percutaneous closure; pulmonary hypertension; systematic review

2.1.2 Introduction

Congenital heart disease (CHD) is the most common type of birth defect worldwide, accounting for almost one-third of all congenital anomalies (94). Atrial septal defect (ASD) is the most prevalent adult CHD with an estimated prevalence of 84 per 100 000 Canadian adults (16). ASD is further classified based on anatomic and physiological characteristics with secundum ASD accounting for about 70% of observed cases (15).

ASDs typically yield a systemic-to-pulmonary (or left-to-right) shunt at the level of the inter-atrial septum. The direction of blood flow, change in magnitude, and degree of shunting is determined by both the size of the defect and the difference in diastolic compliance between the two ventricles (95). Hemodynamically significant left-to-right shunts can lead to right atrial enlargement, tricuspid valve regurgitation (TR), and increased pulmonary blood flow (96). Pulmonary over circulation may cause pulmonary vascular remodelling characterized by increased levels of pulmonary vascular resistance (PVR), and changes in pulmonary arterial pressure (PAP) (97). These changes may result in atrial arrhythmias, right ventricular dilation, right heart failure, and/or pulmonary hypertension (PH) (98). Closure of an ASD is indicated and has been shown to be beneficial in the presence of hemodynamically significant shunts that cause right sided chamber enlargement and that have led to reduced functional capacity (56). While the presence of severe PH is a contraindication for ASD closure, some patients may undergo pre-treatment with PH-specific pharmacotherapy prior to closure, a strategy known as “treat and repair” (71).

As per 2018 American College of Cardiology/American Heart Association (ACC/AHA) and 2016 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines, pulmonary hypertension has been defined as the haemodynamic state of having a mean pulmonary arterial pressure (mPAP) of at least 25 mmHg at rest (1, 56). The term PH encompassed many different clinical classifications, including pulmonary arterial hypertension (PAH). PAH, or pre-capillary PH, was defined as the presence of PH, combined with a pulmonary capillary wedge pressure of <15 mmHg and PVR of ≥3 Wood units (56). The distinction between PH and PAH is important; while all cases of PAH are forms of PH, the

presence of PH may be due to other causes than PAH. Patients with PH related to a CHD have increased morbidity and mortality (59, 99). In February 2018, the 6th World Symposium on Pulmonary Hypertension (WSPH) Task Force proposed changes to existing definitions; namely, to use a lower mPAP cut off of > 20mmHg to define PH and to use pulmonary vascular resistance ⩾3 Wood Units as the only criteria to define pre-capillary PAH (6).

Although ASD closure in adults with normal mPAP and functional capacity is widely accepted as being safe and clinically beneficial, the long-term outcomes and benefits among this population are not clear (46, 100). The most recent ACC/AHA guideline stated that adult CHD patients with PH have a poorer prognosis than those who do not have PH (56). There are a set of recommendations for ASD repair in PH patients depending on the clinical scenario (56). The clinical presentation of PAH typically falls within a spectrum; at one end there are adults with mild pulmonary vascular disease (PVD) and large ASD shunts; these patients can safely undergo ASD closure (11). As a general rule, when systolic PAP (sPAP) is less than one half of systemic blood pressure, and if Qp:Qs is >1.5:1, ASD closure is recommended (56). At the other end are patients with irreversible PVD, leading to shunt reversal and cyanosis; a condition known as Eisenmenger syndrome. Eisenmenger physiology does not respond well to closure, and its presence is a contraindication to closure. When sPAP is greater than two thirds systemic, and Qp:Qs is less than 1, the shunt should not be closed (56). Proper classification of patients within this continuum should be made by a specialist and individual patients should be evaluated on a case by case basis (1). While some studies report that ASD closure in patients with PH is associated with better long-term outcomes (e.g., reduction of atrial arrhythmias, improved cardiac function capacity of PH severity) (101), others report that subsets of patient develop PH or suffer from persistent PH following closure (10, 92). This variability could be partially explained by the effect of the pre-existing PH severity (e.g., PVR or PAP levels) on observed outcomes.

Historically, open-heart surgical closure had been the standard of care for ASD repair. Since the first non-invasive closure of an ASD performed in 1976 (49), percutaneous closure has grown in popularity for its minimal invasiveness and lower complication rates (48, 53). Starting from early to mid 2000s, more than 90% of ASD closures are percutaneous (102), while surgical closure is

reserved for primum, sinus venosus, coronary sinus ASDs or secundum ASDs with the presence of other congenital or acquired cardiac conditions or where significant economic limitations make surgical closure more feasible (56). Differential indication criteria between surgical and percutaneous ASD closure may lead to differences in patient outcomes including those with PH. Whereas where the populations are the same undergoing both therapies the long term outcomes of ASD closure on PH should be similar, there is little data to support this hypothesis.

Overall, information on the long-term effects of percutaneous closure among ASD patients with and without a diagnosis of PH is both limited and variable (56). The aim of this systematic review and meta-analysis was to describe currently used PH definitions, evaluate the prevalence of PH and the effect of PH on outcomes in ASD patients undergoing percutaneous closure.

2.1.3 Methods

Protocol and registration

The reporting of this systematic review followed the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) statement (103). The systematic review protocol has been registered with PROSPERO (registration number: <pending>).

Eligibility criteria

We included studies that reported the prevalence of PH (based on study specific definitions) and/or mean PAP (mPAP or sPAP) levels at baseline and after percutaneous closure of ASD in adult patients over the age of 18 years old. Studies with a mixed patient population were excluded if they did not provide separate data for adult patients with percutaneous ASD closure and only reported pooled data (e.g., a surgical cohort, pediatric population, patients undergoing closure for other congenital heart diseases such as ventricular septal defect, atrioventricular septal defect, or patent foramen ovale).

Clinical outcomes of interest following ASD closure were not limited and included any one of the following: successful closure, survival, New York Heart Association (NYHA) functional class, cardiovascular outcomes (e.g., stroke, myocardial infarction, and heart or lung transplant) and device-related complications. Since the cut offs for pulmonary artery pressure for PH

diagnosis were not defined consistently, we also reported the definitions, PH measurement methods and cut offs that were used by the authors of each study.

We included case series, cohort studies and randomized control trials of any follow-up duration. Single case studies, case series with less than five patients and case-control studies were excluded. We excluded studies that used simulated data sets, reviews, editorials, clinical guidelines, as well as non-human, non-English studies and conference abstracts.

Information sources

Eligible studies were identified through a search of three interdisciplinary databases including Ovid MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from their inception dates to July 13th, 2019.

Search strategy

Our peer-reviewed search strategy was guided by an information specialist experienced in this area. The search syntax combined terms for atrial septal defect, percutaneous closure and pulmonary hypertension (please see Supplemental Table S1 for the search strategy in Ovid MEDLINE). Citations were imported and de-duplicated in a citation manager software.

Study selection

Records identified through our search were screened for potential inclusion in our systematic review using the Covidence online tool (104). Two reviewers (SA and VV) independently screened the titles and abstracts for inclusion. If there was an uncertainty based on the title and abstract of a reference, it was passed through to full text screening. All discrepancies were resolved by reaching a consensus with the two reviewers. Reasons for exclusion were recorded in Covidence.

Data collection and items

Two reviewers in pairs (SA, VV and BH), independently extracted data from included full-text studies using a standardized data extraction form in Excel spreadsheets. Data extraction domains included general study characteristics (e.g. time periods, study design), baseline patient

characteristics before ASD closure (e.g. age, sex/gender, PH definition and prevalence, echocardiographic data, ASD size, NYHA functional class), follow-up data after ASD closure (e.g. mean follow-up time, PH prevalence, echocardiographic data), any vasodilator medications for PH before and after the procedure, and all short and long-term outcomes reported.

Quality assessment

Methodological quality assessment of the included studies was completed using the Joanna Briggs Institute (JBI) Critical Appraisal checklists for cohort and case series studies (105). We adhered to the explanations and definitions provided in the tool and modified the components to make them more specific to our study population when relevant (see Supplemental Table S2). Measurement of the exposure and outcome was considered to be valid when the gold standard of right heart catheterization (RHC) was used (56). We assumed that a dropout rate greater than 20% can be a potential threat to internal validity.

Data analysis and synthesis of results

We undertook an initial descriptive analysis of the included studies by summarizing information on study and patient characteristics (e.g. demographics, ASD information, PH diagnostics, and echocardiographic data before percutaneous closure and outcomes after follow-up). For studies that included PH prevalence before and after ASD closure, we descriptively plotted these values.

Meta-analysis was performed if outcomes of interest were reported in similar patient populations and study designs. We used the *metafor* package in R statistical software for meta-analysis (106). A meta-analysis of PH prevalence before and after ASD closure was completed for studies that reported relevant data. We calculated a combined prevalence value with associated 95% confidence interval (95% CI) using the DerSimonian-Laird random effects model (107). If the individual study estimates for prevalence were between 20% to 80%, then the data were likely to be normally distributed (108). We analyzed the heterogeneity of the prevalence of PH between studies using the I^2 statistic (109).

We measured the effect of percutaneous ASD closure on mean sPAP by calculating the standardized mean differences (SMD) before and after closure. We used SMD to estimate the

effect size of percutaneous closure on mean sPAP values within studies, and to determine a combined pooled effect, for cohort studies and case series separately. We also completed an age-stratified analysis for SMD among younger (<60 years old) and older (>60 years old) patient populations.

2.1.4 Results

Study selection

Our search strategy identified 1,423 potentially relevant records (see Supplemental Figure S1). After removing duplicates, a total of 1,138 records were title and abstract screened. We retrieved 66 studies for a full-text review and excluded 51 studies. The most common reasons for exclusion were poster presentations and/or conference proceedings (n=13), using surgical closure (n=11), and having only pooled results from pediatric and adult populations (n=10). We included a total of 15 studies in this review that met our study eligibility criteria (71, 77-88, 90, 91).

Systematic review

We identified a recent systematic review with a potential overlap with our review (110). A systematic review by Zwijnenburg and colleagues reported the prevalence of PAH among patients undergoing ASD closure, in 30 studies published before March 2017. The review, however, evaluated surgical and percutaneous closure populations together. We limited our inclusion to patients undergoing percutaneous closure considering the current differences in indication criteria for each approach. Zwijnenburg and colleagues included studies that reported RVSP and used the values as proxy for sPAP (i.e., used the two measures interchangeably in their analyses). While RVSP can be used to approximate sPAP, there must be an evidence of no right ventricular or pulmonary tract obstruction (111). The discordance between these two measures is especially pronounced among patients with PH (112). For these reasons, we refrained from seeking studies that reported only RVSP and using that as a proxy for sPAP. We did, however, include studies that reported sPAP measures derived from tricuspid regurgitation jet velocity using the Bernoulli equation. Zwijnenburg's review also combined all forms of PH under PAH, however the importance of this distinction and additional hemodynamic parameters required for its identification have been well emphasized in the AHA guidelines (56), ESC guidelines (1) and by the recent WSPH Task Force (6). In our review we maintained the two as

distinct forms of PH and specified when applicable. Finally, the analyses by Zwijnenburg were limited to descriptive summaries and no meta-analysis was performed. In our review we present both a descriptive summary and a formal meta-analysis.

Study characteristics

The 15 included studies represented 12 different countries including three from Canada, two from Japan, and one study for each of the following countries: The Netherlands, Germany, India, Spain, Austria, Belgium, Italy, Taiwan, China, and Israel. Six of the included studies were case series and nine were cohort (four retrospective and five prospective) studies (Table 1A). The studies represented a total of 1,073 adult patients undergoing percutaneous ASD closure. Sample sizes among studies ranged from six to 215 patients before ASD closure. The mean age was between 29 to 67 years, with a range from 20 to 81 years. On average, females comprised 61.5% to 87.0% of the study samples. Mean follow-up time varied from three to 60 months.

PH measurement and definitions

Twelve studies (80%) used transthoracic (TTE) or transesophageal echocardiography (TEE), and four studies used the gold standard, RHC (71, 79, 88, 90). The definitions for PH varied among studies (Table 1A). Nine studies used sPAP values to define PH with cut-off values of ≥35 (77, 85), ≥40 (78, 81, 83, 84, 87, 88), or ≥60 mmHg (90). One study defined mild (sPAP = 40–49), moderate (50–59) and severe (sPAP ≥60) PH levels (80). One study used used mPAP > 25 mmHg (79) and another used either sPAP≥60 or mPAP≥25 mm Hg to define PH (71). Three studies did not report the cut off values (82, 86, 91). From 15, six (40%) studies reported measuring PAH (71, 80, 81, 83, 85, 90), although not all of these studies mentioned measuring capillary wedge pressure (CWP) explicitly. None of the studies used mPAP >20 mmHg as a cut-off value to define PH.

Five studies reported PH prevalence before the procedure and at follow-up after the procedure (77, 81, 82, 84, 87). Twelve studies reported mean sPAP before and after closure (Table 1B) (71, 78-81, 83-86, 88, 90, 91). The case series exclusively enrolled patient populations with an existing diagnosis of PH (71, 78-80, 88, 90). All studies reported the mean ASD diameter and method of PH assessment. Data on NYHA functional class was available for 13 of the included

studies (71, 77-88), and all 13 studies reported an improvement in in NYHA functional class following closure. The proportion of patients in class III or IV ranged from 1.3% to 88% before closure and 0% to 5% after closure.

Quality assessment

The results of the quality appraisal of included cohort studies is presented in the Supplemental Figure 2. All cohort studies recruited patients with and without PH from the same population and all patients underwent PH measurement. Three studies used RHC to assess for PH before and after closure (71, 88, 90). One study used TTE at baseline and switched to RHC at follow up (79). Eight (89%) of cohort studies had greater than 20% loss to follow-up. Reasons for loss to follow-up were explained in six (67%) studies, and strategies to deal with loss to follow-up were applied in 3 (33%) studies.

The quality assessment of six case series studies is shown in the Supplemental Figure 2B. All studies that used RHC were case series. One of the included case series used RHC to collect patient data at baseline, then switched to TTE at follow-up.

Prevalence of PH before and after closure

Five cohort studies reported PH prevalence before and after ASD closure using study-specific mean PAP or mean sPAP cut offs. The prevalence of PH varied from 24% to 62% before ASD closure and from 5% to 31% after ASD closure (Figure 1). The reported prevalence estimates among the included studies were between 20% and 80%, as such, we assumed our data was normally distributed and did not apply a transformation for potential outliers when meta analyzing.

The pooled PH prevalence was 44% (95% CI 29% - 60%) before closure (Figure 2 A**)** and 18% (95% CI 8% - 27%) after closure (Figure 2 B**)**. The between study heterogeneity was high (I^2 = 93% and 91% respectively (P < .01)).

Mean sPAP before and after ASD closure

The mean follow-up time in the studies ranged from 10 to 60 months. A total of 12 studies reported mean sPAP before and after closure. Of the 12 studies, three reported mean sPAP values stratified by age (83, 86, 91) while one study reported outcomes by PH specific medication groups (i.e. patients taking PH specific medications and patients not taking PH specific medications) (71).

We calculated the SMD for two different types of patient populations: cohort studies that enrolled a general patient population with and without PH (Figure 3 A), and case series studies that exclusively enrolled patients with PH (Figure 3 B). In cohort studies, the mean sPAP ranged from 30 to 53 mmHg before closure, and from 25 to 43 mmHg after closure. All cohort studies showed a reduction in sPAP following closure, with a positive SMD of 1.12 (95% CI 0.81, 1.44). In case series studies, the mean sPAP ranged from 51.6 to 102.6 mmHg before closure and from 21 to 55.7 mmHg after closure. All case series reported a reduction in sPAP following ASD closure with a pooled SMD of 1.62 (95%CI 1.00, 2.23). Between study heterogeneity was high in both sets of analyses (I^2 = 83% in cohort and 71% in case series).

For cohort studies we also completed exploratory age-stratified subgroup analyses for mean sPAP by analyzing the studies with younger (≤60 years old) and older patient populations (>60 years old) separately. The pooled SMD among the younger and older patients were 1.25 (95% CI 0.78, 1.71) and 0.91 (95% CI 0.56 to 1.27), respectively (Figures 4A and B). A small improvement in between study heterogeneity was observed.

Long-term outcomes

The reporting of long-term outcomes was limited and non-consistent between the studies in term of types of outcomes and length of follow-up (see Supplemental Table S3 for details). None of the included studies compared the outcomes of ASD closure between patients with and without PH.

2.1.5 Discussion

To our knowledge this is the first systematic review and meta-analysis exclusively assessing the effects of percutaneous ASD closure on PH in adults. We included a total of 15 studies that

reported baseline and follow-up data on PH in this patient population. We found that the PH prevalence as well as mean sPAP decreased following ASD closure among all studies, irrespective of age. The magnitude of mean sPAP reduction was greater amongst case series studies which could potentially suggest that patients with high PH may benefit the most from the intervention. A high degree of heterogeneity was observed between the studies, and long-term outcomes were reported inconsistently.

Quality assessment

The critical appraisal of the methodological quality of studies revealed areas of concerns. Case series were relatively more rigorously done than the cohort studies, perhaps due a more defined approach to case selection. Overall, only three studies used RHC for PH assessment contributing to variability in PH prevalence estimates, and therefore, heterogeneity between the studies. Another area of concern was the adequacy of follow-up with roughly half of the included cohort studies having more than 20% loss to follow-up of their original sample. Depending on the reasons of loss to follow-up, the true effect of ASD closure on PH measures and other outcomes can be over- or underestimated.

Measurement of PH

Although RHC is the current gold standard for hemodynamic data collection, it is costly, invasive and less desirable by patients. Thus, echocardiographic methods were predominantly used in included studies. Echocardiography may suggest the presence of PH by estimating the RVSP; however, it cannot differentiate between the two types of PH associated with ASD, PH (mPAP ≥25mmHg and PVR < 3 wood units) and PAH (mPAP ≥25mmHg and PVR ≥3 wood units) (1, 56). A PH diagnosis using RHC is necessary to distinguish PH subtypes and, therefore, we limited our use of the term PAH. Furthermore, echocardiographic studies used variable cut offs for PH definition and diagnosis ranging from mPAP >25 mmHg to sPAP >35, 40, 50, or sPAP >60 mmHg. Although there is an established strong linear relationship between mPAP and sPAP, the proposed formula of $mPAP = 0.61\ sPAP + 2\ mmHg$ to link them is based on RHC measures only (113) which does not consider the additional variability introduced by using TEE or TTE (114). For consistency and due to the limited reporting of a few studies, all values reported in this review were for mean sPAP in patients. We contemplate that some portion of

between study heterogeneity we observe was due to difference in PH measurement methods and definitions. Future studies should use guideline recommendations to measure and define PH to enhance the comparability between the studies and validity of findings.

Definition of PH

The ESC clinical guidelines for PH, and the AHA/ACC guidelines for congenital heart disease proposed the same case definitions and cut-offs for PH and PAH; PH is defined as mPAP ≥ 25 mm Hg, and PAH is defined as mPAP ≥25mm Hg combined with a pulmonary capillary wedge pressure of ≤15 mmHg and PVR of ≥3 Wood units (1, 56). As we observed, these definitions were not consistently applied in the current literature. For example, as stated, six studies reported results for PAH; however, only two studies applied the current guideline definition for PAH. This could be partially explained by the fact that PH guideline definitions require RHC to retrieve hemodynamic parameters while most included studies used echocardiographic methods. The latter is a more practical approach if one wants to use the same PH definition before and after the procedure without performing the invasive RHC twice. The recent WSPH redefined PH as mPAP >20 mmHg, and PAH as mPAP >20 with PVR of ≥3 Wood units (6); these changes will be reflected in the new ESC guidelines (6). The new PH definition and cut-off is predicted to increase the PH population estimates by less than 10% (115). To accelerate research in this area and to investigate the effect of this change on real world patient outcomes, authors should start consistently applying the new PH definition. One way to achieve this would be the development of a validated formula to link the RHC-based PH definition to an echocardiography-based definition.

PH prevalence before and after ASD closure

We found that the combined PH prevalence declined from 44% at baseline to 18% following the closure within a mean follow-up range of 15 to 60 months. PH prevalence widely varied among the included study populations. A Dutch study following 882 ASD patients for a mean follow-up of 4.2 years showed similar changes in PAH prevalence from 35% before closure to 13% after closure (59, 116). In our review, studies that reported a high PH prevalence after closure had smaller sample sizes. Our meta-analyses also showed a high degree of heterogeneity between the studies. Therefore, the results should be interpreted with caution considering the small sample

size of existing PH prevalence studies. It is also important to note that we are using the term prevalence to report the proportion of PH following percutaneous closure. However, in absence of patient level data, we cannot differentiate whether these are newly developed incident cases of PH or cases of persistent PH. This becomes necessary when determining attributing factors associated with the development or persistence of PH.

Mean sPAP before and after ASD closure

To ensure that the change we observed in mean sPAP values could be attributed to ASD closure and not to individual patient characteristics, we chose to separate our analyses by patient population and age. When we separated our meta analyses by study design, we saw less heterogeneity among case series studies compared to cohort studies. We found that patients in the case series with a higher mean sPAP at baseline demonstrated greater differences in sPAP in follow-up. Case series studies also showed a greater combined mean sPAP reduction than cohort studies. This could be because patients with a higher baseline sPAP (extreme cases) have more room for improvement or regression to the mean. Although all studies reported an overall reduction in mean sPAP, two studies mentioned that a small proportion of individual patients did not show a decrease in sPAP (71, 80). One study reported outcomes separately for patients taking PH specific medications who showed better improvement in sPAP following closure compared to patients not on PH medications (71). The study concluded that the use of PH medications can increase the magnitude of sPAP reduction following ASD closure.

All cohort studies that provided age stratified mean sPAPs reported reductions irrespective of age category. However, the magnitude in SMD reductions were typically larger in cohorts that had a lower mean age. As such, we chose to analyse age cohorts separately and explore this association. Previous literature has indicated an association between age and pulmonary hypertension (117-119). With the current data from this review, we distinguished young patients from older patients by applying an age cut-off of 60 years. We categorized each study population as young or old based on their mean (SD) age at baseline, falling either above or below 60 years. For the study by Yong et al. which had a mean age of 54 years (standard deviation = 16), we completed a series of sensitivity analyses by adding this study to the younger cohort, older

cohort, or removing it, respectively. We ultimately added it to the older population age group based on lowest heterogeneity.

Current guidelines indicate percutaneous closure of ASD is beneficial at any age (117). We found positive mean sPAP reductions following ASD closure within age stratified cohorts, meaning that percutaneous closure of an ASD is beneficial in lowering mean sPAP levels, at any age. These results are consistent with the findings of other studies (83, 86, 91). In our meta-analysis we saw a decrease in mean sPAP reduction beyond the age of 60 in both of the age stratified cohorts. Although percutaneous closure lowers mean sPAP levels in all age cohorts, the magnitude of this effectiveness may decrease with older age.

2.1.6 Conclusions

In conclusion, we found that the pooled prevalence of PH and mean sPAP among patients who were eligible and underwent ASD closure decreased after the procedure. The decrease was observed in all age groups, to a difference degree. Long term follow-up studies are needed to observe the effect of change in PH on outcomes. A more consistent approach to diagnose and define PH is warranted to enhance the comparisons between studies. Prospective studies should use the new PH diagnostic criteria and evaluate the impact of this change on patient outcomes.

Acknowledgements

We are grateful to Ashley Farrell (Library and Information Services, University Health Network, Toronto, ON, Canada) for her advice and support in generating and executing the search.

Funding sources

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Table 1A. Study and patient characteristics at baseline, before ASD closure (n = 15)

	Study design	Time period	Sample size (n)	Age (years)	% Female	ASD diameter (mm)	NYHA class III-IV (%)	PH assessment method	PH measure and cut offs (mmHg)	Mean sPAP (mmHg)	PH prevalence (%)
Veldtman, 2001*	Retrospective cohort	1997-1999	40	38 (20-71)	75	13 ± 4	5	TEE	sPAP >35	NR	62
De Lezo, 2002	Case series	NR	29	56 ± 14	83	26 ± 7	48	TTE/TEE	sPAP ≥40	64 ± 23	100
Bruch, 2007	Case series	NR	15	66 (48-77)	66.6	22.7 ± 7.0 (9-34)	60	TTE/RHC	mPAP>25	58.3 ± 15	100
Balint, 2008 †*	Case series	1999−2004	54	59 ± 15	76	18 ± 7	41	TTE/TEE	sPAP 40–49 (mild), 50–59 (moderate), ≥60 (severe)	58 ± 10	100
Yong, 2009 †*	Prospective cohort	1999−2006	215	54 ± 16	73	19 ± 6	19	TTE	sPAP ≥40	30.0 [25.0, 36.0]	50.2
Yalonetsky, 2009 *	Retrospective cohort	1998−NR	23				NR	TTE	sPAP cut off NR		NR
Age 40 - 60yrs				52 ± 6	74	19 ± 5				39 ± 7.7	
Age 60+yrs				67 ± 5	70	18 ± 5				53 ± 16.2	
Altindag, 2010	Retrospective cohort	1999-2008	47	58 ± 13 (40-79)	79	NR	43	TTE/TEE	NR	NR	62
Humenberger, 2011 †*	Prospective cohort	NR						TTE/TEE	sPAP ≥40		NR
Age < 40yrs			78	29 ± 6.7	61.5	23 [29, 26]	1.3			31±7	
Age 40-60yrs			84		65.5		3.8			37± 10	
Age > 60yrs			74		82.4		41.4			53 ± 17	

				50 ± 5.6 71 ± 6.1		22 [17.5, 26.5] 22.5 [20, 28]					
Huang, 2012 †	Retrospective cohort	2007-2010	15	32.3 ± 12.8	73.3	NR	NR	RHC	sPAP ≥60 (severe PAH)	51.6 ± 9.4	100
Kefer, 2012 *	Prospective cohort	1999−2009	112	46 ± 17	71	PH: 22 ± 5 no PH: 18 ± 6	31	TTE	sPAP >40	47 ± 7	28
Nakagawa, 2012 †*	Prospective cohort	2005-2010	30	75.8 ± 3.8 (70–85)	66.6	20.3 ± 6.4	35	TEE	mPAP ≥25	35.6 ± 11.8	53
Mangiafico, 2013 *	Prospective cohort	2008-2011			NR	NR		TTE	sPAP cut off NR		NR
Age < 40yrs			10	29 ± 7.3			0			35.1 ± 6.6	
Age > 40yrs			20	58 ± 11			0			41.2 ± 6.4	
Akagi, 2015 †	Case series	2006-2014						RHC			100
PHM group 1			8	37 ± 15	100	22±7	88		sPAP ≥60	60 ± 11	
non-PHM group 2			14	66 ± 13	71	23±8	21		mPAP ≥25	58 ± 17	
Wang, 2017	Retrospective cohort	2000-2009	179	53 [40-81]	75.4	NR	8.9	TEE	sPAP ≥40	44.8 ± 22.2	24
Dalvi, 2019	Case series	2009-2014	6	29 ± 8.89	83.3	28±2.09	0	RHC	mPAP ≥25	102.6 ± 11.5	100

IQR, interquartile range; mPAP, mean pulmonary artery pressure; NA, not applicable; NR, not reported; NYHA, New York Heart Association; PHM, pulmonary hypertension medication; RHC, right heart catherization; sPAP, systolic pulmonary artery pressure; TEE-transesophageal echocardiography; TTE, transthoracic echocardiography.

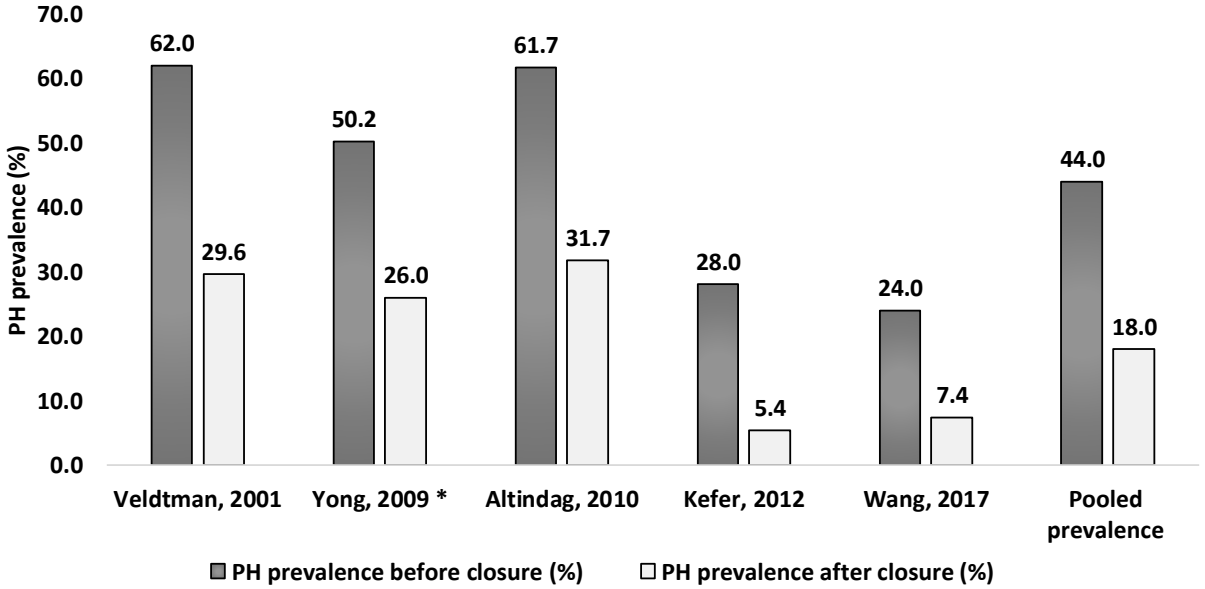
When relevant, values were reported as mean ± SD, mean ± SD (range), mean (range), or median [IQR].
* Study reported sPAP values derived from RVSP.
† Study reported values for PAH.

Table 1B. Study reported outcomes at follow-up (n = 15)

	Sample size (n)	Mean follow-up time (months)	PH assessment method	Mean sPAP after closure (mmHg)	Mean sPAP reduction (mmHg)	PH prevalence (%)	NYHA class III-IV (%)
Veldtman, 2001	27	NR (1-12)	TTE	NR	10*	28.5	0
De Lezo, 2002	28	21 ± 14	TTE	34 ± 11	14*	100	0
Bruch, 2007	13	10 ± 4	RHC	49.9 ± 17.8	NR	92	0
Balint, 2008 †	39	31 ± 15	TTE/TEE	44 ± 16	14*	NR	20
Yong, 2009†	186	15 [8-43]	TTE	25.0 [24, 49]	5 [1 -13]	26	3.7
Yalonetsky, 2009			TTE		NR	NR	NR
Age 40- 60yrs	NR	NR (1-12)		26			
Age 60+yrs				33.5			
Altindag, 2010	41	15 ± 15	TTE/TEE	NR	NR	38	5
Humenberger, 2011 †		28 ± 19	TTE			NR	
Age < 40yrs							
Age 40-60yrs	75			26 ± 5	5± 8		0
Age >60yrs	84			30 ± 6	8± 9		0
	74			43 ± 14	9± 14		4
Huang, 2012† ‡	7	23.4 ± 9.7	RHC/TTE	21.0 ± 3.8	16*	13	NR
Kefer, 2012	112	60 ± 34	TTE	31 ± 11	7*	5.4	8
Nakagawa, 2012 †	27	19.1 ± 11.3	TEE	27.2 ±7.3	NR	NR	4
Mangiafico, 2013		NR (1-12)	TTE			NR	
Age < 40yrs	10			28 ± 2.8	7.1*		0
Age >40yrs	20			28.4 ± 6.5	12.8*		0
Akagi, 2015 †		19 ± 27 (3–83)	TTE		NR	NR	
PHM group 1	8			40 ± 9			0
non-PHM group 2	14	19 ± 16 (4–61)		38 ± 10			0
Wang, 2017	176	45.6 ± 25.2	TEE	NR	NR	7	1.7
Dalvi, 2019	4	39.5 ± 8.5	RHC	55.7 ± 9.2	12.8*	NR	0

NR, not reported; NYHA, New York Heart Association; PHM, pulmonary hypertension medication; RAD, right atrium diastolic size; RHC, right heart catherization; sPAP- systolic pulmonary artery pressure; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

* When mean sPAP reductions were not reported, we calculated [Mean sPAP before closure (mmHg)] – [Mean sPAP after closure (mmHg)]
When relevant, values were reported as mean ± SD, mean (range), or median [IQR].
† Study reported values for PAH.
‡ Study reported mean values as mPAP



*Study reports pulmonary arterial hypertension (PAH).

Figure 1. PH prevalence before and after ASD closure presented in each study

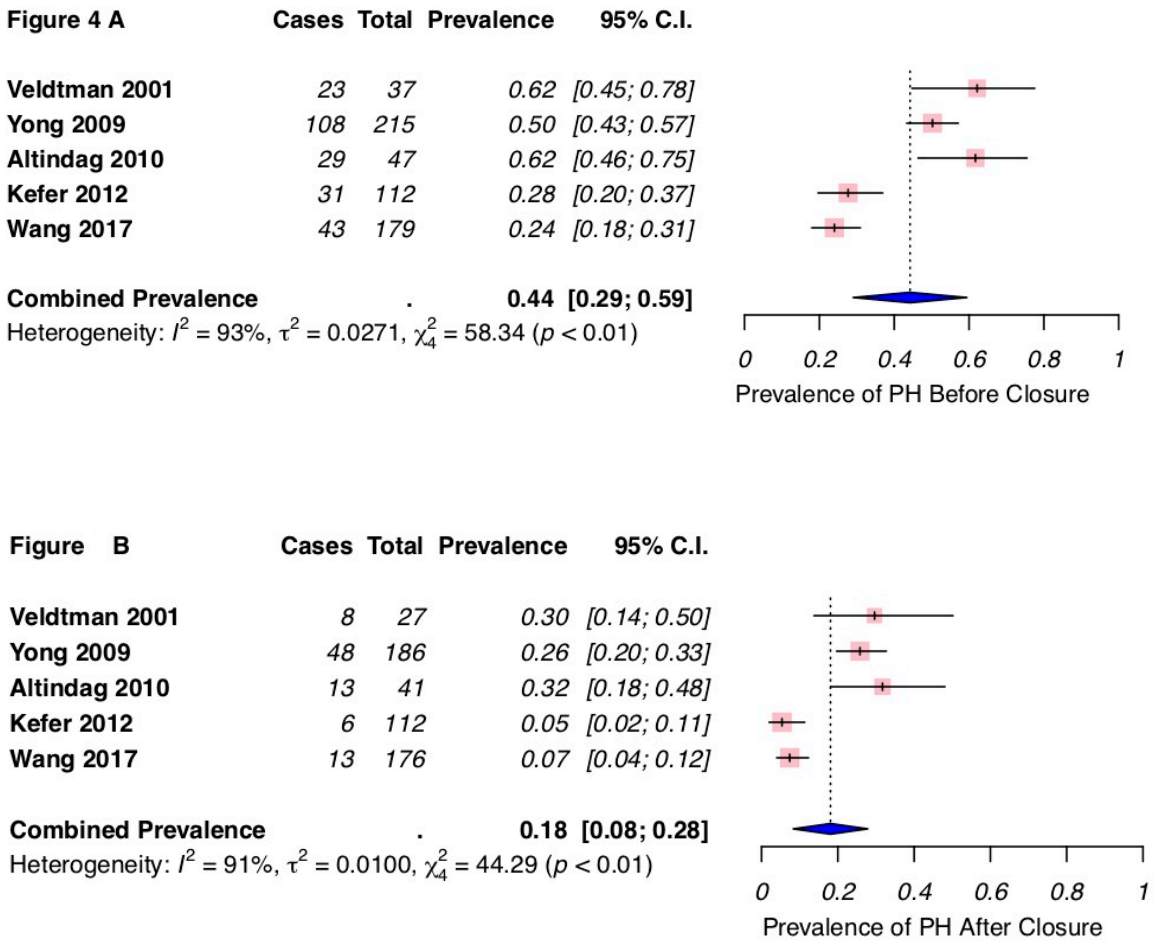


Figure 2. The pooled PH prevalence before **(2A)** and after **(2B)** ASD closure in cohort studies

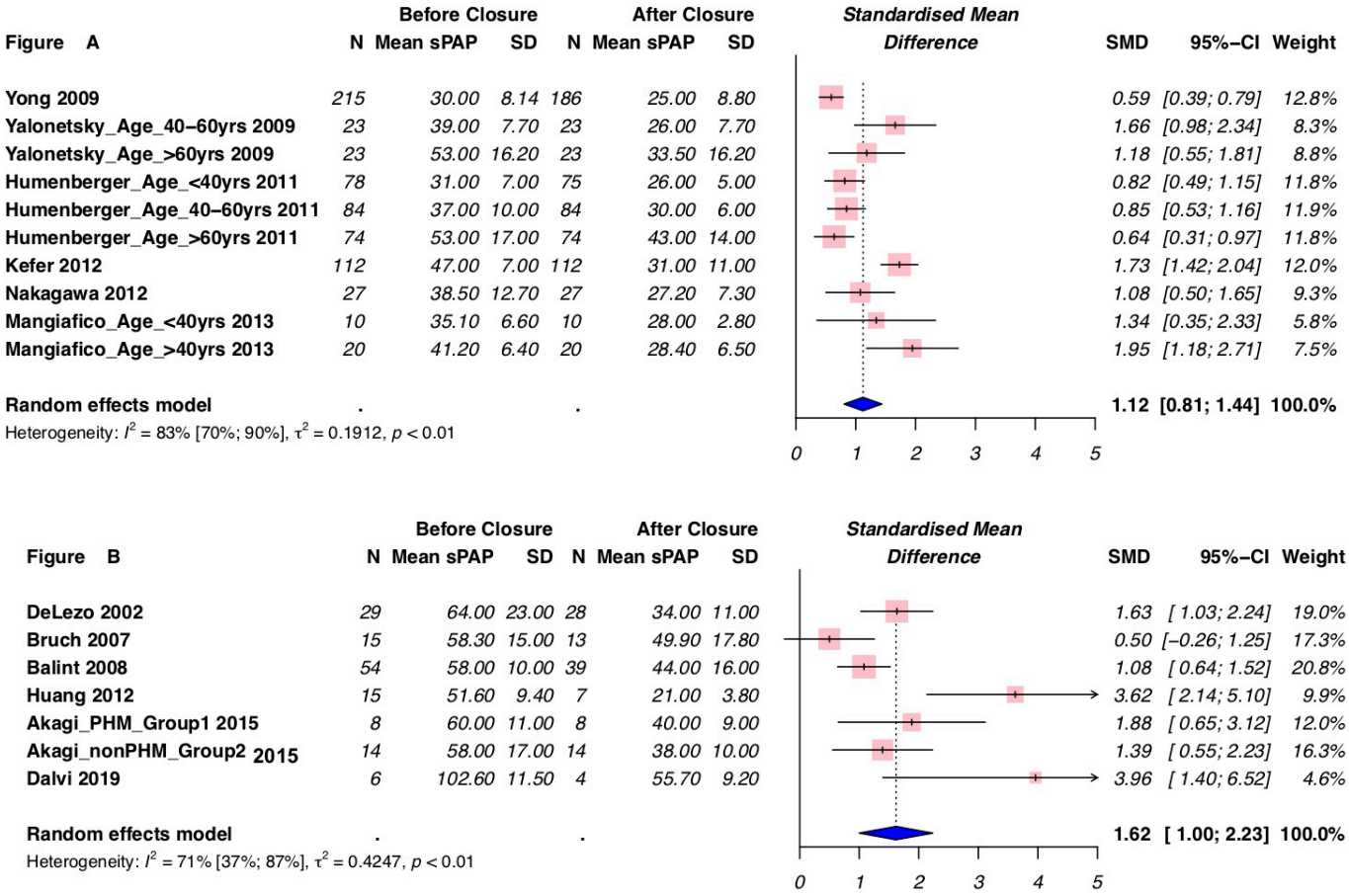


Figure 3. Standardized mean difference in mean sPAP before and after ASD closure, **(3A)** in cohort studies, **(3B)** in case series

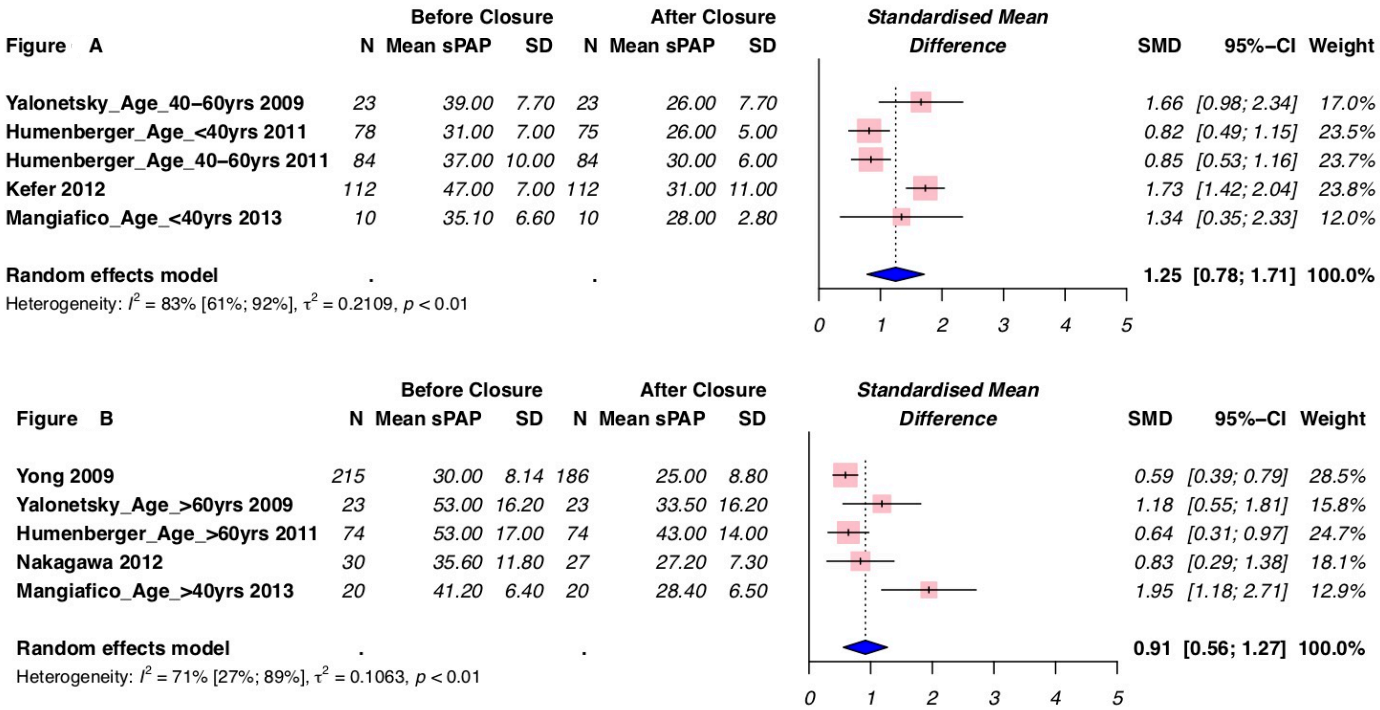


Figure 4. Standardized mean difference in mean sPAP before and after ASD closure among cohort studies, **(4A)** in younger patients and **(4B)** in older patients

2.1.7 Supplementary materials

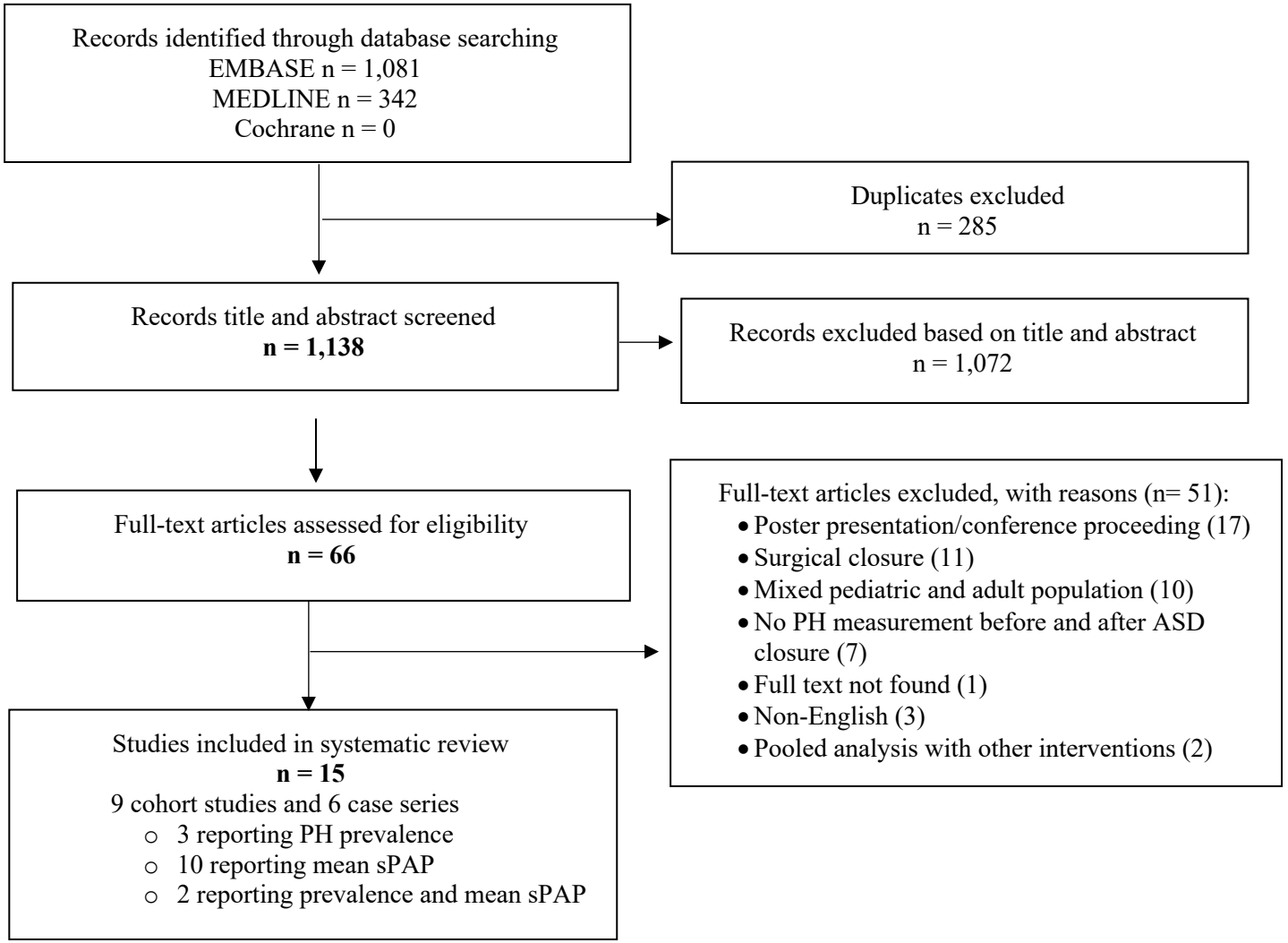
Supplemental Table S1. Literature search syntax

MEDLINE SEARCH
Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®, 1946 to Present.
Date: July 13th, 2019
Limits: none

#	Searches	Results
1	Heart Septal Defects, Atrial/	12112
2	(atria* adj4 sept* adj4 defect*).mp,kw.	16764
3	(atria* adj2 sept* adj2 shunt*).mp,kw.	94
4	(interatria* adj3 sept* adj3 defect*).mp,kw.	357
5	(interatria* adj2 sept* adj2 shunt*).mp,kw.	10
6	(atrium adj2 sept* adj2 defect*).mp,kw.	33
7	(atrium adj2 sept* adj2 shunt*).mp,kw.	0
8	(cleft* adj2 heart* adj2 atrium*).mp,kw.	0
9	(secundum adj2 defect*).mp,kw.	380
10	(ostium adj2 secundum).mp,kw.	622
11	(primum adj2 defect*).mp,kw.	170
12	(ostium adj2 primum).mp,kw.	329
13	or/1-12	17060
14	Cardiac Catheterization/	47101
15	Septal Occluder Device/	2475
16	"Prostheses and Implants"/	44806
17	limit 16 to yr="1997 - 2009"	11150
18	(transcatheter* adj4 (closure? or intervention? or treatment? or procedure? or device? or method? or approach?? or technique? or occlus* or repair* or percutaneous)).mp,kw.	7503
19	(trans-catheter* adj2 (closure? or intervention? or treatment? or procedure? or device? or method? or approach?? or technique? or occlus* or repair* or percutaneous)).mp,kw.	123
20	(percutaneous adj5 (closure? or intervention? or treatment? or procedure? or device? or method? or approach?? or technique? or occlus* or repair*)).mp,kw.	68084
21	(device? adj7 (closure? or occlud*)).mp,kw.	7148
22	occluder?.mp,kw.	5914
23	amplatzer.mp,kw.	2744
24	cardio-o-fix.mp,kw.	11
25	cardia-atriasept.mp,kw.	0
26	cardiastar.mp,kw.	3
27	cardia-star.mp,kw.	3
28	cardiaseal.mp,kw.	0
29	cera.mp,kw.	463

30	clamshell.mp,kw.	363
31	das angel wing?.mp,kw.	10
32	intrasept.mp,kw.	8
33	memopart.mp,kw.	1
34	starflex.mp,kw.	96
35	star-flex.mp,kw.	1
36	gorehelex.mp,kw.	1
37	helex.mp,kw.	96
38	cardioform.mp,kw.	16
39	biostar.mp,kw.	86
40	figulla.mp,kw.	59
41	or/14-15,17-40	131259
42	Hypertension, Pulmonary/	33078
43	(Pulmonary adj3 hypertensi*).mp,kw.	51195
44	(Lung? adj3 hypertensi*).mp,kw.	1171
45	(Pulmonary adj3 high blood pressure?).mp,kw.	20
46	(Lung? adj3 high blood pressure?).mp,kw.	18
47	42 or 43 or 44 or 45 or 46	51523
48	13 and 41 and 47	342

Supplemental Figure S1. Flow diagram of literature search and selection of studies



Supplemental Table S2. Quality Assessment Checklist

JBI Critical Appraisal Checklist for Cohort studies*

1. Were the two groups similar and recruited from the same population
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups
3. Was the exposure/outcome (PH) measured in a valid and reliable way? (Did they use RHC?)
4. Were confounding factors identified
5. Were strategies to deal with confounding factors stated
6. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
7. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored? (was <20% of the original sample loss to follow-up?)
8. Were strategies to address incomplete follow-up utilized?
9. Was appropriate statistical analysis used?

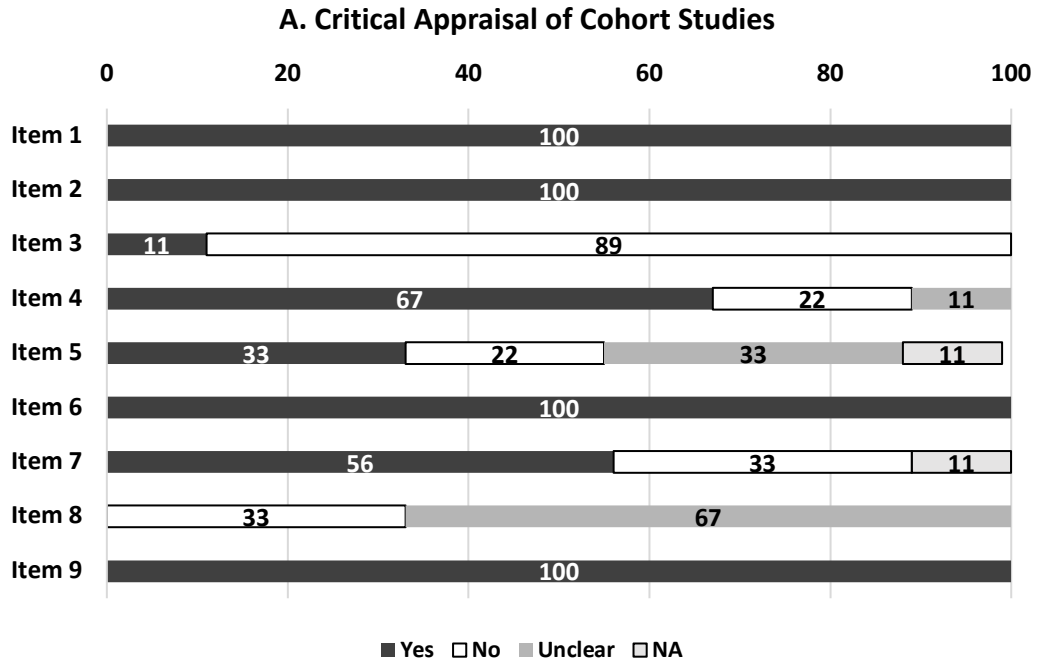
*Since we were interested in PH before and after the intervention, we joined the original items 3 and 7 into one (item 3 here). For the same reason, we also excluded the original item 6 that was asking if the participants were free of the outcome at the start of the study.

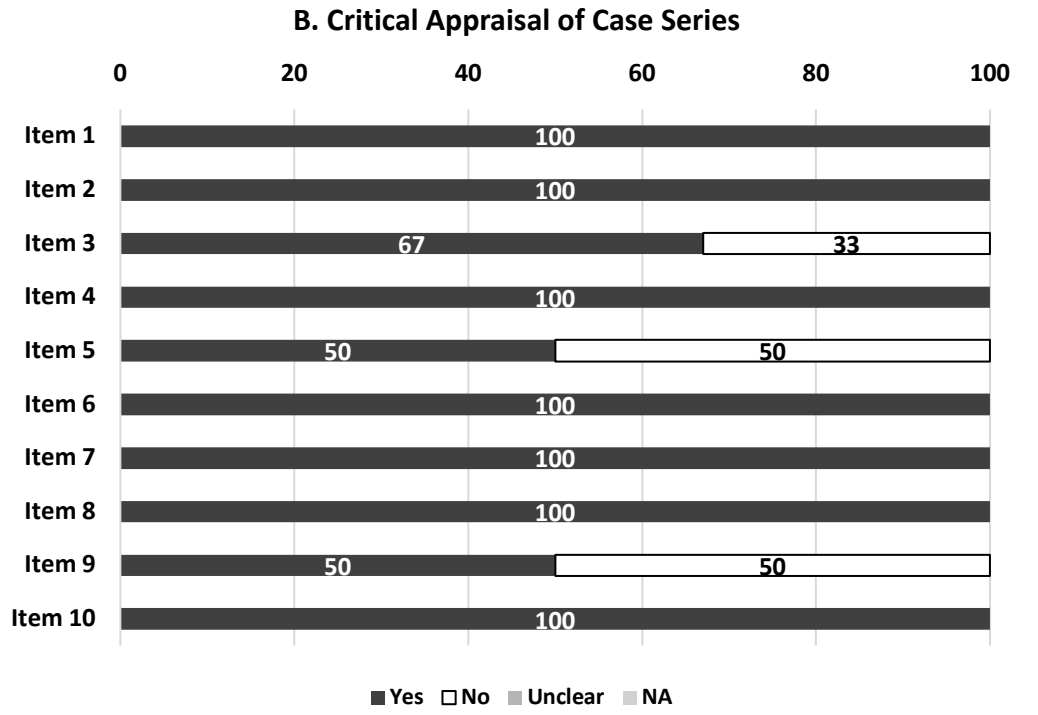
JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series? (Did they use RHC?)
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow-up results of cases clearly reported?
9. Was there clear reporting of the presenting clinics demographic information?
10. Was statistical analysis appropriate?

Full checklists available at: https://joannabriggs.org/critical_appraisal_tools

Supplemental Figure S2. Results from JBI critical appraisal checklist, **(A)** in cohort studies, **(B)** in case series





Supplemental Table S3. Additional details on study characteristics

Study, Year	RVSP before closure (mmHg), Mean, (SD)	RVSP after closure (mmHg), Mean, (SD)	Cardiac medications	Reported outcomes
Veldtman, 2001	NR	NR	NR	Successful ASD closure in 100% of patients; residual shunts detected in 73% of patients after closure; persistent elevation of PA pressures and persistent RV enlargement at 1-year of follow-up in 29% of patients.
De Lezo, 2002	NR	NR	NR	Successful ASD closure in 100% of patients; a significant reduction in the percentage of patients with AF after repair (from 41% to 24%) at the mean follow-up of 21 ± 14 months.
Bruch, 2007	11.6 (4.9)*	9.4 (4.6)*	NR	Successful ASD closure in 100% of patients.
Balint, 2008	57 (11)	51 (17)	NR	At the late follow-up of 31 ± 15 months, 5% of patients died; overall mean RVSP decreased at late follow-up, but only 43.6% of patients had normalisation (<40 mm Hg); 15.4% of patients had persistent severe PAH.
Yong, 2009	NR	NR	NR	Successful ASD closure in 194/215 (90.2%), complete closure in 133/215 (71.5%) of patients, and a proportional reduction in atrial tachyarrhythmias of 37.5% at the median follow-up of 15 months (IQR 8 to 43).
Yalonetsky, 2009	NR	NR	NR	No significant TR observed in any patients at the latest follow-up of 12 months.
Altindag, 2010	NR	NR	Oral anticoagulants (n=13), antiplatelet drugs (n=8), beta-	Successful ASD closure in 100% of patients; minor complications occurred in 10% of patients; at mean follow-up time of 15 months, 7% died

Study, Year	RVSP before closure (mmHg), Mean, (SD)	RVSP after closure (mmHg), Mean, (SD)	Cardiac medications	Reported outcomes
			blockers (n=20), ACE inhibitors (n=10), diuretics (n=9), statins (n=5), cardiac glycosides (n=6), other medications (n=23)	during follow-up; 7% required surgical reintervention.
Humenberger, 2011	9 (7,11)*	NR	NR	At early follow-up (< 3 months) successful ASD closure was reported in 100% of patients. After 5 years of closure, one patient developed a large thrombus, three cerebral events were observed, two patients with an ischaemic event, one patient receiving oral anticoagulation for AF had minor cerebellar bleeding.
Huang, 2012	NR	NR	NR	NR
Kefer, 2012	47 (7)	47 (8)	NR	No recurrent stroke; symptoms reported before the procedure improved in 88% of patients; freedom from death, cardiac surgery or recurrent embolism was 99% at 1-year and 98% at 5-year follow-up.
Nakagawa, 2012	40.8 (6.0)*	31.6 (4.5)*	Diuretics, warfarin, antihypertension and anti-arrhythmia drugs	Successful ASD closure in 93% of patients; 8% had residual shunt and 8% died at a mean follow-up of 19.1 ± 11.3 months; pacemaker implantation in 4%; left ventricular remodeling and TR improvement reported.
Mangiafico, 2013	23.1 (4.7)**	23.7 (3.5)**	NR	At 12 months of follow-up, 63% of patients experienced feelings of fatigue, 77% reported headaches and dyspnea, 57% insomnia, and 87% palpitations;

Study, Year	RVSP before closure (mmHg), Mean, (SD)	RVSP after closure (mmHg), Mean, (SD)	Cardiac medications	Reported outcomes
				significant reductions in RVEDD, RAD, RV MPI, sPAP and LVEDD.
Akagi, 2015 **PHM group 1** **Non-PHM group 2**	NR	NR	Endothelinreceptor antagonists Bosentan (n=5), ambrisentan (n=2), phosphodiesterase type-5 inhibitors (sildenafil (n=5), tadalafil (n=1)), beraprost (n=3), epoprostenol (n=3) None	No adverse events were observed.
Wang, 2017	NR	NR	NR	At early follow-up of 3 months, 13% of patients developed new onset arrhythmia; 74% of these patients returned to normal sinus rhythm at 12 months of follow-up, 2.3% of patients developed persistent AF, and 8.7% required a pacemaker.
Dalvi, 2019	NR	NR	All the patients were put on Sildenafil and/or Bosentan at least 3 months before device closure of the ASD.	All patients reported significant symptomatic improvement; reversed remodeling of the right atrium and the right ventricle was seen in all the patients at mean follow-up of 39.5 ± 8.5 months.

ACE, Angiotensin-converting enzyme; AF, atrial fibrillation; IQR, Interquartile range; LVEDD, left ventricle end-diastolic diameter; NR, not reported; PAH, pulmonary arterial hypertension; PHM, pulmonary hypertension medication; RAD, right atrium diastolic size; RVEDD, right ventricle end-diastolic diameter; RV MPI, right ventricle myocardial performance index; RVSP, right ventricular systolic function; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

*Estimates for right ventricular end diastolic pressure.

**Estimates for tricuspid annular plane systolic excursion.

Chapter 3. Cohort Study

3.1 Long-term Outcomes in Adult Patients with Pulmonary Hypertension After Percutaneous Closure of Atrial Septal Defects

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Short title: ASD closure outcomes in pulmonary hypertension

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3.1.1 Abstract

Background

Pulmonary hypertension (PH), recently redefined as mean pulmonary arterial pressure (mPAP) > 20 mmHg, may be observed in patients with atrial septal defects (ASD). Long-term outcomes of percutaneous atrial septal defect (ASD) closure in patients with PH remain unclear. We aimed to determine the effect of preprocedural PH status on procedural and long-term outcomes among patients undergoing ASD closure.

Methods

Study population was selected from a large retrospective registry that included adult patients who underwent percutaneous ASD closure from 1998 to 2016 at a single centre in Toronto. We included only the patients who had right heart catheterizations at the time of the index procedure. This clinical registry was linked to provincial, population-based administrative databases to capture information on short- and long-term outcomes.

Results

We included a total of 632 ASD closure patients who had right heart catheterization data, of whom 359 patients (56.8%) had PH. The mean follow-up length was 7.6 years (standard deviation [SD] = 4.6 years). Patients with PH had a higher mean age ($p<0.001$) and a higher prevalence of comorbid conditions than those without PH including hypertension (54.3% versus 21.6%, $p<0.001$), diabetes (18.1% versus 5.9%, $p<0.001$), and chronic obstructive pulmonary disease (17.3 versus 7.3, $p<0.001$). Based on the adjusted Cox proportional hazards model, patients with PH had a significantly higher risk for developing a composite outcome of major adverse cardiac and cerebrovascular events (MACCE) (heart failure, stroke, myocardial infarction, or cardiovascular mortality), with an adjusted HR of 2.45 (95% CI = 1.38, 4.37). No significant differences were found in hazards of developing new onset AF and all-cause mortality in adjusted analysis. When using the prior cut-off (mPAP ≥ 25 mmHg), the risks of developing any of these outcomes were significantly higher in the PH group.

Conclusions

ASD patients with PH undergoing closure suffer from more comorbidities and worse long-term MACCE outcomes, compared to patients without PH. The use of the new PH definition potentially dilutes the effect of this serious condition on outcomes in this population.

Key words: pulmonary hypertension, atrial septal defect, outcomes, survival

3.1.2 Introduction

Atrial septal defect (ASD) is the second most common form of congenital heart disease lesion (CHD) accounting for 8–10% of all heart defects, with an estimated prevalence of 1.64 per 1000 live births (94). Increased pulmonary blood flow from significant left-to-right shunts can lead to right atrial enlargement, atrial arrhythmias, and pulmonary hypertension (PH) (96). Based on increasing rates of pulmonary hypertension in Ontario, PH has been identified as an emerging public health epidemic (120).

Among the cardiovascular sequelae, PH has been associated with increased morbidity and mortality in patients with a clinically significant ASDs (98, 99, 121). PH is characterised by vasoconstriction and remodelling of pulmonary arteries, leading to pulmonary vascular disease and right heart failure. When the right-sided overload is present, early intervention and ASD closure is recommended (56). Percutaneous closure is the preferred therapeutic modality of choice for ASD occlusion over surgical closure due to its lower complication rates and less invasive nature (48, 53, 122). The effect of ASD closure on PH however is still controversial with some reports indicating a lowering of pulmonary arterial pressure among patients with PH (77, 80, 81, 91, 101, 123) and some reporting about a subset of patients who develop PH or suffer from persistent PH after closure (10, 92). Reports comparing long-term outcomes between patients with and without PH after percutaneous ASD closure are highly limited. Our targeted search identified only one such study (124); based on that study PH patients had higher comorbidity burden at baseline and worse survival after percutaneous ASD closure among patients > 48 years old compared to patients without PH.

Previously, the 5th World Symposia on Pulmonary Hypertension (WSPH), the 2018 American College of Cardiology/American Heart Association (ACC/AHA), and the 2016 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines, defined PH as presence of a mean pulmonary arterial pressure (mPAP) $\geqslant$ 25 mmHg. Pulmonary arterial hypertension (PAH) had been defined as the presence of pre-capillary PH, including pulmonary capillary wedge pressure (PCWP) $\leqslant$ 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood Units (WU) (1, 56). In 2019, the 6th WSPH Task Force proposed an updated haemodynamic definition of PH as mPAP > 20 mmHg and PVR $\geqslant$ 3 WU, and defined PAH as

mPAP > 20 mmHg, PCWP ⩽ 15 mmHg and PVR ⩾ 3 WU (6). The update was based on a meta-analysis of RHC data among healthy individuals (7). The impact of the change in PH definition on patient outcomes has yet to be demonstrated in patients undergoing ASD closure.

Although initial symptoms of ASDs and PH could be nonspecific and attributed to a more common cardiorespiratory disease delaying the diagnosis, the estimated prevalence of PH among ASD patients has been reported to be between 10% (13) to 20% (19, 57, 58). Former estimates are based on a more conservative definition of PH, which may lead to an underestimation of the true burden of PH. Additionally, reports on PH prevalence and outcomes are highly variable and susceptible to over or underestimation depending on the definition of PH and the measurement modality (right heart catheterization [RHC] versus echocardiography) for PH case ascertainment (125).

In this study, we aim to describe and compare the clinical characteristics, procedural, short and long-term outcomes between patients with and without PH after percutaneous closure of ASD, using the updated PH definition and gold standard for PH measurement. In addition, we evaluated the effect of PH definition change on long-term adverse outcomes.

3.1.3 Methods

Study population

The study population included all eligible, consecutive adult patients (≥ 18 years) who underwent percutaneous closure of an ASD at the Peter Munk Cardiac Centre (PMCC) of the Toronto General Hospital (TGH), University Health Network (UHN), Ontario, Canada between 1998 and 2016. These patients were part of a detailed, retrospective clinical ASD registry. PH was defined as mPAP > 20 mmHg during RHC. We thereby excluded patients with incomplete or missing RHC data. The study protocol was approved by the research ethics of the University Health Network (UHN). Individual patient consent was waived due to the retrospective study design and lack of experimental treatment.

Data sources

We used a retrospective clinical ASD registry to identify patients who had undergone ASD closure at the PMCC. The registry was created by abstracting patient data from patient medical records and included data on patient demographics (e.g., age at ASD closure, gender, height, weight), clinical characteristics (e.g., comorbidities, shunt size), and peri-procedural (e.g., pulmonary arterial pressures, device type, length of stay), and follow-up data.

To ascertain post procedural long-term healthcare use and outcomes, data from the ASD clinical registry was linked to Ontario population-based databases held at ICES (Institute for Clinical Evaluative Sciences). ICES is a prescribed entity under section 45 of the Ontario's Personal Health Information Protection Act, which can securely collect and store patient health information in databases (e.g., the Canadian Institute for Health Information [CIHI] hospital Discharge Abstract Database [DAD] captures hospitalizations, the Ontario Health Insurance Program [OHIP] database captures outpatient physician claims). Patients from our ASD clinical registry were linked to ICES health administrative databases using their OHIP number and assigned a unique ICES key number (IKN) to maintain anonymity. An IKN is derived from Ontario health card numbers and exists for every Ontario resident who has been eligible for health care. Patients were excluded if they had an invalid IKN, were not linkable, or were non-Ontario residents.

Variable definitions and study outcomes

The primary exposure of interest was pulmonary hypertension at the time of percutaneous ASD closure defined as mPAP > 20 mmHg measured using RHC (6). Baseline characteristics (sex, age, year of intervention, echocardiographic parameters) were retrieved from the ASD clinical registry. Baseline comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease [COPD], coronary artery disease [CAD], stroke, atrial fibrillation [AF], malignancy, prior myocardial infarction [MI], heart failure [HF], renal failure, cancer, Charlson comorbidity index [CCI] $\geqslant$ 1) were retrieved by applying a two-year look back period from the index procedure date, using validated health administrative case definitions and algorithms applied in ICES databases (Appendix A, Table A1).

Procedural outcomes (i.e. residual leaking and procedural complications defined as vascular complications, need for urgent surgery or blood transfusions, and device embolization or erosion) were identified using the ASD clinical registry, Short term outcomes (e.g. 30 day hospitalization or emergency department [ED] visits, length of stay for the index date procedure), and long-term outcomes (acute myocardial infarction [AMI], new onset atrial AF, AF hospitalization, new onset HF, HF hospitalization, stroke, new pacemaker implantation, any open heart surgery, any atrial septal defect surgery, all-cause mortality, and cardiovascular mortality) were identified and defined using ICES databases (Appendix A, Table A2). A composite outcome for major adverse cardiac and cerebrovascular events (MACCE) was defined as an occurrence of new congestive heart failure, stroke, acute myocardial infarction, and cardiovascular (CV) mortality.

Patient follow up began the day of percutaneous ASD closure (index date) until the last available date in ICES databases; December 31st, 2016 for CV mortality and MACCE, and December 31st, 2018 for all other outcomes.

Statistical analysis

Statistical analysis was performed using R statistical software, version 3.4.1 (114). We performed descriptive analyses of patients undergoing ASD closure with and without pulmonary hypertension for baseline characteristics and outcomes as relevant. Continuous data were presented as mean and standard deviation (SD) and categorical data were presented as counts and percentages.

Comparisons of baseline characteristics between patients with and without PH were performed using the chi-square test or Fisher's exact test as relevant. Long-term outcomes were compared between groups using Poisson regression and were reported as events per 1,000 person years (PY). Long-term survival was evaluated using the Kaplan-Meier method, and between-group differences were analyzed using the log-rank test. Multivariable Cox proportional hazards models were used to compare the hazard of developing adverse outcomes (i.e., all-cause mortality, MACCE, and atrial fibrillation) between patients with and without PH at the time of closure. Proportional hazards assumption was assessed using Schoenfeld residuals. Baseline

covariates were chosen based on results from univariable analyses and clinical relevance. P values < 0.05 were considered to indicate statistical significance. Small cells with ≤ 5 observations were suppressed, as per ICES privacy regulations. As sensitivity analyses, we evaluated outcomes using the former PH cut-off values, by PH severity levels, by PH categories, and after excluding patients with heart failure at baseline.

3.1.4 Results

Selection of study sample

A total of 1,502 eligible adult patients underwent ASD closure at the PMCC between 1998 and 2016 (Figure 1). After excluding 112 patients who had invalid or non-linkable IKNs the resulting sample included 1,390 patients that were successfully linked to ICES databases. Among the 1,390 patients, 758 patients had undergone echocardiography and 632 had undergone RHC. The comparison of the baseline characteristics from these two patient populations are reported in Appendix B. Patients who underwent RHC were significantly older, had higher BMI, and higher prevalence of comorbid conditions at baseline (i.e. tricuspid regurgitation, hypertension, diabetes, COPD, CAD, atrial fibrillation, heart failure, and CCI ⩾ 1).

Patient characteristics

Based on mPAP > 20 mmHg, 56.8% (n = 359) of patients undergoing ASD closure had PH. Baseline patient characteristics by PH status are summarized in Table 1. In the total sample, the mean age was 50.7 years (standard deviation (SD = 17.5)), 32.1% were male, 40.2% had hypertension, 27.8% CAD, and 15.5% AF. Statistically significant differences in several baseline characteristics were observed between patients with and without PH. Patients with PH, for example, were significantly older (56.5 versus 43.1 years), had higher prevalence of moderate to severe tricuspid regurgitation (34.2% versus 8.9%), hypertension (54.3% versus 21.6%), and AF (19.5% versus 10.3%), when compared to patients without PH at baseline. All reported baseline invasive (from RHC) or echocardiographic hemodynamic parameters, with the exception of cardiac output, were significantly different between patients with and without pulmonary hypertension at baseline (Appendix C).

Short-term outcomes

Any type of procedural complication occurred in 1.7% of patients with no significant difference between the groups. Residual leaking occurred in 5.1% of patients with no significant difference between patients with or without PH. In the total sample, 27 (4.5%) patients had a LOS > 1 day following ASD closure, and 115 (19.4%) patients had a hospitalization or emergency department visit within 30 days after the index date of ASD closure. There were no statistically significant differences between patients with and without PH for these short- term outcomes ($p > 0.05$, data not shown).

Long-term outcomes

Long-term outcomes in the full sample and stratified by PH status are presented in Table 2. The mean follow-up length was 7.7 years (SD = 4.7 years) for the full sample, 7.4 (4.3) years for PH and 8.2 (5.1) years for patients without PH ($p = 0.037$). In the full sample of patients, the most common long-term outcomes were AF hospitalizations (n = 87, 13.8%), new onset AF (n = 85, 13.4%), MACCE composite outcome (n = 86, 13.6%), and all-cause mortality (n = 67, 10.6%). Statistically significant differences in the rates of adverse events were observed between patients with and without PH for AF hospitalization (25.8 versus 8.9 hospitalizations per 1,000 PY), new onset AF (22.3 versus 12.1 events per 1,000 PY), HF hospitalization (8.1 versus 0.9 hospitalizations per 1,000 PY), new onset HF (11.5 versus 3.1 events per 1,000 PY), MACCE composite outcome (26.2 versus 8.0 events per 1,000 PY), all-cause mortality (19.6 versus 7.1) and CV mortality (7.7 versus 0.9) per 1,000 PY. Table 2 shows the results of the unadjusted Cox proportional hazard regression. With the exception of AMI, permanent pacemaker implantation, and open-heart surgery, all long-term outcomes that were evaluated were found to be significantly increased when PH was present in unadjusted analyses. Multivariable models were not developed for each adverse outcome because of the small number of individual outcomes considering the small incidence of these outcomes, except for new onset AF, MACCE, and all-cause mortality.

Unadjusted Kaplan Meier curves for all-cause survival for the full sample and by PH status is shown in Figure 2. Results from the unadjusted and adjusted Cox proportional hazards models for new onset AF, MACCE composite outcome and all-cause mortality are shown in Table 3. Based on univariate analysis, age, hypertension, diabetes, and COPD, were significantly

associated with PH status, new onset AF, MACCE, and all-cause mortality. Two adjusted models were built, Model 1 which adjusted for age only, and Model 2 which adjusted for age, hypertension, diabetes, COPD and AF. Patients with PH had a significantly higher risk of developing AF in the unadjusted model (HR = 2.44, 95%CI = 1.52, 3.90) but not after adjustment. Patients with PH had a significantly higher risk for developing MACCE composite outcome in the unadjusted model (HR = 5.22, 95%CI = 3.13, 9.08) and after adjustment in Model 1 (HR = 2.73, 95%CI = 1.53, 4.85), and Model 2 (HR = 2.11, 95%CI = 1.17, 3.81). Patients with PH had a higher hazard of all-cause mortality in the unadjusted model (HR = 2.96, 95%CI = 1.68, 5.22). After adjustment, in both models, PH status was no longer associated with all-cause mortality.

Effect of PH definition change on PH prevalence and outcomes

In a sensitivity analyses, we applied the former, mPAP ⩾ 25 mmHg cut-off value to define PH. With this approach, the number of patients with PH decreased from 359 to 231 patients or from 56.8% to 36.6% of PH prevalence in the study sample. Appendix D shows the unadjusted survival for all-cause mortality (Figure D), and the results from unadjusted and adjusted Cox proportional hazards models (Table D). In unadjusted Cox proportional hazards models, PH patients had an increased hazard of developing new onset AF, MACCE, and all-cause mortality. In adjusted analyses, both in Models 1 and 2, patients with PH continued to have significantly higher hazards of developing adverse outcomes than those without PH. Based on multivariable Model 2, the hazard ratio was 1.73 (95%CI = 1.09, 2.75) for developing new onset AF, 1.89 (95%CI = 1.18, 3.02) for MACCE and 1.53 (95%CI = 0.02, 2.55) for all-cause mortality.

Evaluation of PH severity on all-cause mortality

To further test the effect of PH severity on outcomes, we grouped all patients that received RHC into three categories by mPAP categories: 0-20 mmHg indicating no PH, 21-24 mmHg indicating borderline PH, and ≥ 25 mmHg indicating definitive PH. Appendix E shows the results from unadjusted and adjusted Cox proportional hazards models (Table E), and the unadjusted survival curves for all-cause mortality (Figure E). In the unadjusted Cox proportional hazards model, patients with mPAP ≥ 25 mmHg had a significantly higher risk of all-cause

mortality than those in 0-20 mmHg category (HR = 3.60, 95%CI = 2.01, 6.43). No differences were found by PH severity after adjusting for age and additional baseline comorbidities.

As another sensitivity analysis, we evaluated the effect of PH categories on all-cause mortality among the patients for whom we had data on PCWP. Appendix F shows the unadjusted survival curves for all-cause mortality (Figure F) and results from unadjusted and adjusted Cox proportional hazards models (Table F). There were no significant differences in the risk of all-cause mortality between PH categories in unadjusted and adjusted analysis. We noted a high level of missingness in this parameter.

We also evaluated the effect of PH on all-cause mortality after excluding patients with heart failure at baseline (Appendix G). The unadjusted survival curves for all-cause mortality (Figure G) showed statistically significant difference in survival among patients with and without PH after excluding patients with HF at baseline, similar to results in original analysis. There were no significant differences in the hazards rates for all-cause mortality in the adjusted analyses (Table G), similar to results in original analysis.

3.1.5 Discussion

To our knowledge, the present study is among one of the largest sample size studies with the longest follow-up in adult ASD population with PH. This is also the first study applying the new PH definition in ASD closure patients and also evaluating the effect of this change on clinical outcomes. We found that ASD patients with PH at baseline presented with more comorbid conditions and experienced higher rates of adverse long-term outcomes, including MACCE, than patients without PH. PH status, however, did not have a negative effect on the overall survival.

Patient sample and characteristics

We present findings from a population of 632 ASD patients with RHC data and a mean follow-up time of 7.7 years. A recent systematic review evaluating PH before and after percutaneous ASD closure in adults found 15 studies with sample sizes varying from six to 215 patients, mean follow-up time varying from three months to five years, and from 15 only 3 studies used RHC for PH diagnosis (125). Demographically, the mean age of our study population, 50.7 (SD =

17.5) years, was similar to other ASD cohorts (81, 84, 87, 124). The sex ratio of our ASD cohort was also consistent with previously published findings (79, 82, 85, 124).The prevalence of PH in our cohort was higher than other large ASD cohorts in which the prevalence varied from 24% to 50% (81, 84, 87). This could be explained by our use of the new definition for PH and RHC. In our study, the change in PH cut off increased PH prevalence by 20.3%.

We found that ASD patients with PH were different from patients without PH in several prognostically important clinical characteristics, with PH patients presenting with a higher burden of baseline comorbidities. Similar to our ASD cohort, previous studies also reported significant differences in baseline characteristics between patients with and without PH with respect to ASD shunt size (19, 126), age at closure (81, 83), BMI, and hypertension (81, 124, 127). Characteristics of past studies that compare patients with and without PH are reported in Appendix H. In addition, we found hypertension, diabetes, COPD and AF to be significant risk factors for adverse outcomes in ASD closure patients. Therefore, as confounders, these comorbidities were considered in our adjusted analyses.

Long-term outcomes

Given the lack of literature, available studies are heterogenous in comparison of long-term outcomes between ASD closure patients with and without PH. Although adverse events were rare, we reported large differences in event rates by baseline PH status with significantly higher rates among patients with PH. We found high rates of new onset AF in our patient population overall (15.9%). A recent synthesis of 5 studies (n = 466) assessing new onset AF in patients undergoing percutaneous ASD closure reported a pooled proportion of AF in 4.9% patients (95% CI = 1.69%,11.7%) (46). In our study, the incidence of new AF was significantly higher in patients with PH in unadjusted analysis however, it became non-significant after adjusting for confounders. Past studies of PH in ASD closure populations have reported both decreased incidence of new AF and proportion of pre-existing AF following closure (78, 81).

All-cause mortality over a mean follow up of 7.7 years was observed in 10.6% of the total sample. Previous estimates of all-cause mortality in patients undergoing ASD closure ranged from 7-8% during average follow-up from 1.6 to 7.4 years (82, 85, 124). We found a significant

hazard ratio of 2.96 (95% CI = 1.68, 5.22) for all-cause mortality in patients with PH compared to patients without PH; however, this became non-significant in the adjusted analysis. The only prior study of comparative survival reported that patients > 48 years old with preprocedural PH undergoing percutaneous closure of ASD had an increased risk of mortality compared to those without (Appendix H); however, it reported only the unadjusted results and used the prior PH cut-off of mPAP ⩾ 25 mmHg (124).

We defined the MACCE composite endpoint as development of a heart failure, stroke, myocardial infarction, or CV mortality and found that patients with PH had a significantly higher risk of MACCE in both unadjusted and adjusted analyses. In this composite outcome, heart failure was the most common event, followed by stroke and CV mortality. We were unable to find a prior study in this population reporting a similar MACCE outcome.

Diagnosing pulmonary hypertension

RHC is the gold standard to establish PH diagnosis and its severity. Due to its invasive nature, however, it is not routinely conducted in ASD patients to diagnose PH. At our center, RHC has been increasingly used during the ASD closure starting from the early 2000's due to the decreasing surgical closure rates and the shift towards percutaneous closure. This was reflected in our comparison of baseline characteristic between patients with and without RHC in our original sample. Patients who received RHC were generally sicker; with higher average age, BMI, and increased prevalence of comorbidities (i.e. tricuspid regurgitation, hypertension, diabetes, COPD, CAD, AF, heart failure, and CCI ⩾ 1). This may be because of differential indication criteria for RHC prior to its use becoming routine practice. Between 2008 and 2016, RHC was performed in 72% of ASD patients who had closure.

RHC is the only modality available to confirm the presence of PH after an echocardiography detects a potential PH. It has been well documented that echocardiography is frequently inaccurate in estimating pulmonary artery pressures (10, 128, 129). Therefore, guidelines state that PH cannot be reliably defined by echocardiography and an RHC must be performed to confirm the diagnosis (1). A recent study by Fauvel and colleagues used the new definition for PH and found poor agreement between mPAP values derived from RHC and corresponding

tricuspid regurgitation peak velocity from echocardiography (128). They report that a lower echocardiography cut off for the diagnosis of PH may potentially lead to a 111% increase in RHC demand to confirm PH. By using both RHC and the updated PH cut off, the results from the present study are both reflective of the current population and generalizable to future populations of PH patients undergoing ASD closure.

The updated hemodynamic definition of PH was proposed by the 6th WSPH based on recent emerging evidence. In our cohort, applying the updated definition substantially increased the number of patients diagnosed with PH by 20.3% (from 36.6% to 56.8%). Although this is the first study applying the revised definition for PH diagnosis in ASD patients, previous data from other cohorts report the prevalence of PH to increase by a lesser degree. Jaafar and colleagues assessed the impacts of the new PH cut off in a cohort of patients with scleroderma and reported that the prevalence of PH increased by 2.6% (from 51.1% to 53.7%) (130). While a recent study found the prevalence and incidence of PH in Ontario to be on the rise (120), we found that applying the new cut off for PH will further increase the prevalence estimates in ASD patients. With the new cut-off, a number of patients shift from the "borderline PH" range (mPAP between 21 and 24 mmHg) to now being classified as having PH. It has been reported that patients with borderline PH suffer poorer prognosis, more similar to patients with mPAP $\geqslant$ 25mmHg (4, 7). Following growing evidence and more studies showing poorer outcomes amongst patients with borderline PH, guidelines lowered the mPAP cut off value for PH. In our own sensitivity analyses, however, we found that the all-cause mortality was not significantly different in patients with borderline PH compared to those with no PH in both unadjusted and adjusted analysis.

We compared the effect of the new definition of PH, mPAP > 20 mmHg, with the prior cut off, mPAP $\geqslant$ 25mmHg. When applying the old cut off, we found statistically significant hazard ratios in all unadjusted and adjusted models for new onset AF, MACCE, and all-cause mortality. When applying the new cut off, only MACCE remained significant in the adjusted models. By using the updated clinical definition for PH, we included a sizeable population of 128 patients with former borderline PH in our PH population. According to our analyses, the implications of an mPAP between 20-24 mmHg at the time of closure on all-cause mortality were insignificant

and adding these patients to our PH population may have caused a dilution in the observed effect of PH on all-cause mortality. The application of the updated clinical definition of PH in patients undergoing ASD closure diminished the potential negative impact of the baseline PH on adverse outcomes in patients undergoing ASD closure. Conversely, lowering the mPAP threshold for PH may allow the early screening, identification, clinical monitoring treatment in patients who may potentially progress to symptomatic PH.

Strengths and limitations

We present findings from one of the largest and longest follow up studies reporting outcomes in clinically defined patients with PH undergoing ASD closure. All patients included in our analyses received RHC to accurately diagnose PH by a member of an experienced team. Due to the retrospective nature of our study, we encountered potential sources of bias. We only included patients with RHC data, potentially introducing a selection bias. Availability of RHC data however reflected current practices; increasingly more patients had RHC after 2008 (68.8%) compared to before (31.2%). Therefore, results from our study may be more generalizable to contemporary cohorts. We used administrative health databases to establish several comorbidities and outcomes potentially introducing some misclassification bias. Administrative databases also lack prognostically important clinical variables. ICES databases have been widely used for health services research and have established standards and algorithms to minimize this bias. We have limited data on PH medication use in the ASD registry and in administrative databases; as such, we were unable to report PH medications used in our cohort. The Ontario Drug Benefit program covers prescription medication in those ≤24 and ≥65 years old. Therefore the Ontario Drug Benefit database at ICES did not contain this information for our full sample Additionally, we did not have RHC measurements at follow-up; therefore, we were not able to assess the effects of closure on PH status through serial mPAP measurements. A recent meta-analysis synthesized the changes in pulmonary arterial pressures before and after percutaneous closure with serial RHC or echocardiographic data in 12 cohort studies and showed a reduction in mean systolic PAP following closure, with a positive standardized mean difference of 1.12 (95% CI 0.81, 1.44) (125).

3.1.6 Conclusions

In conclusion, adult patients with preoperative PH differ in several characteristics from patients without PH at the time of ASD closure. If PH is defined using the new PH cut-off, adults ASD patients with PH undergoing closure had higher hazards in developing the composite outcome of MACCE but not in developing new AF or all-cause mortality. When using the old cut-off, PH patients had higher hazards of developing all the defined adverse outcomes. Further studies are needed to evaluate the impact of the change in PH definition on patient management decisions (e.g., initiation of PH medication, referral for closure), and ultimately on patient outcomes.

Table 1. Baseline characteristics of study population

	Full sample n=632	Pulmonary hypertension		
		No n=273	Yes n=359	P value
Male, n (%)	203 (32.1)	93 (34.1)	110 (30.6)	0.441
Age, mean (SD)	50.7 (17.5)	43.1 (15.8)	56.5 (16.5)	<0.001
BMI (kg/m^2), mean (SD)	26.9 (5.8)	25.6 (5.3)	27.9 (5.9)	<0.001
Shunt (Qp: Qs), mean (SD) †	2.0 (0.8)	1.7 (0.5)	2.2 (0.9)	<0.001
Tricuspid regurgitation, n (%) †				
No/mild	298 (75.8)	150 (91.1)	148 (65.8)	
Moderate/severe	95 (24.2)	18 (8.9)	77 (34.2)	<0.001
Hypertension, n (%)	254 (40.2)	59 (21.6)	195 (54.3)	<0.001
Diabetes, n (%)	81 (12.8)	16 (5.9)	65 (18.1)	<0.001
COPD, n (%)	82 (13.0)	20 (7.3)	62 (17.3)	<0.001
Coronary artery disease, n (%)	176 (27.8)	66 (24.2)	110 (30.6)	0.233
Stroke, n (%)	17 (2.7)	11 (4.0)	6 (1.7)	0.113
Atrial fibrillation, n (%)	98 (15.5)	28 (10.3)	70 (19.5)	0.002
Malignancy, n (%)	11 (1.7)	≤5*	5-9	0.877
Prior MI, n (%)	7 (1.1)	≤5*	≤5	1.000
Heart failure, n (%)	27 (4.3)	≤5*	24-28	<0.001
Renal failure, n (%)	4-8	≤5*	6-8	NA
Cancer, n (%)	11 (1.7)	≤5*	7-11	1.000
CCI ≥1, n (%)	107 (16.9)	33 (12.1)	74 (20.6)	0.006

BMI: body mass index; CCI: Charlson comorbidity index; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; SD: standard deviation.

**Small cells (≤5 observations) suppressed.*

†Data on Qp:Qs was missing in 445 (70.4%) patients (190 non-PH versus. 255 PH) and tricuspid regurgitation in 239 (37.8%) patients (105 non-PH versus. 134 PH). All calculations with these variables were completed after excluding the missing values.

Table 2. Comparison of long-term outcomes between patients with and without PH (unadjusted)

	Full sample n=632	Pulmonary hypertension			Unadjusted Hazard Ratio (95% CI)†	P value
		No n=273	Yes n=359	P value		
Long-term outcomes	**n (%)**	**Event rates per 1,000 PY (95% CI)**				
AMI	12 (1.9)	2.5	1.8	3.1	0.872	1.66 (0.48; 5.62)	0.418
AF hospitalization[a]	87 (13.8)	18.0	8.9	25.8	<0.001	2.97 (1.80; 4.91)	<0.001
New onset AF[b]	85 (13.4)	17.6	12.1	22.3	0.006	2.44 (1.52, 3.90)	<0.001
HF hospitalization[a]	23 (3.6)	4.8	0.9	8.1	0.001	9.33 (2.18; 39.94)	0.003
New onset HF[b]	37 (5.9)	7.7	3.1	11.5	0.001	7.27 (3.14; 16.81)	<0.001
Stroke	22 (3.5)	4.6	1.8	6.9	0.028	4.08 (1.37; 12.15)	0.011
PPI	23 (3.6)	4.8	2.7	6.5	0.141	3.30 (0.91; 5.85)	0.796
Any open-heart surgery	15 (2.4)	3.1	2.7	3.5	1.000	1.30 (0.46; 3.67)	0.627
MACCE composite outcome	86 (13.6)	17.3	8.0	26.2	<0.001	5.22 (3.13; 9.08)	<0.001
All-cause mortality	67 (10.6)	13.9	7.1	19.6	0.001	2.96 (1.68; 5.22)	<0.001
CV- related mortality	22 (3.5)	4.6	0.9	7.7	0.002	10.11 (2.33; 43.92)	0.002

AF: atrial fibrillation; AMI: Acute myocardial infarction; CI: confidence interval; CV: cardiovascular; HF: heart failure; MACCE: major adverse cardiac and cerebrovascular event; PPI: permanent pacemaker implantation; PY: person years.

MACCE defined as heart failure, stroke, acute myocardial infarction, or CV mortality.

[a]Includes hospitalizations both for new (incident) and existing (prevalent) AF and HF patients, respectively.

[b]Number of events and incidence rates were calculated after excluding patients with prior AF (n=98) or prior HF (n=27).

†Patients without PH used as reference population.

Table 3. Cox proportional hazards models for adverse outcomes†

Outcomes	Unadjusted HR (95% CI)	P value	Adjusted Model 1 HR (95% CI)	P value	Adjusted Model 2 HR (95% CI)	P value
New onset AF	2.44 (1.52, 3.90)	<0.001	1.58 (0.95; 2.62)	0.080	1.50 (0.94; 2.39)	0.090
MACCE	5.22 (3.13; 9.08)	<0.001	2.73 (1.53; 4.85)	**<0.001**	2.45 (1.38; 4.37	**0.002**
All-cause mortality	2.96 (1.68; 5.22)	<0.001	1.22 (0.67; 2.22)	0.500	1.15 (0.63; 2.10)	0.650

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular event.

MACCE defined as heart failure, stroke, myocardial infarction, or CV mortality

Model 1: adjusted for age for all outcomes.

Model 2 adjusted for age, hypertension, diabetes, and COPD, and atrial fibrillation for MACCE and all-cause mortality and adjusted for age, hypertension, diabetes and COPD for new onset AF outcome.

†Patients without PH used as reference population.

Figure 1. Study population flow diagram

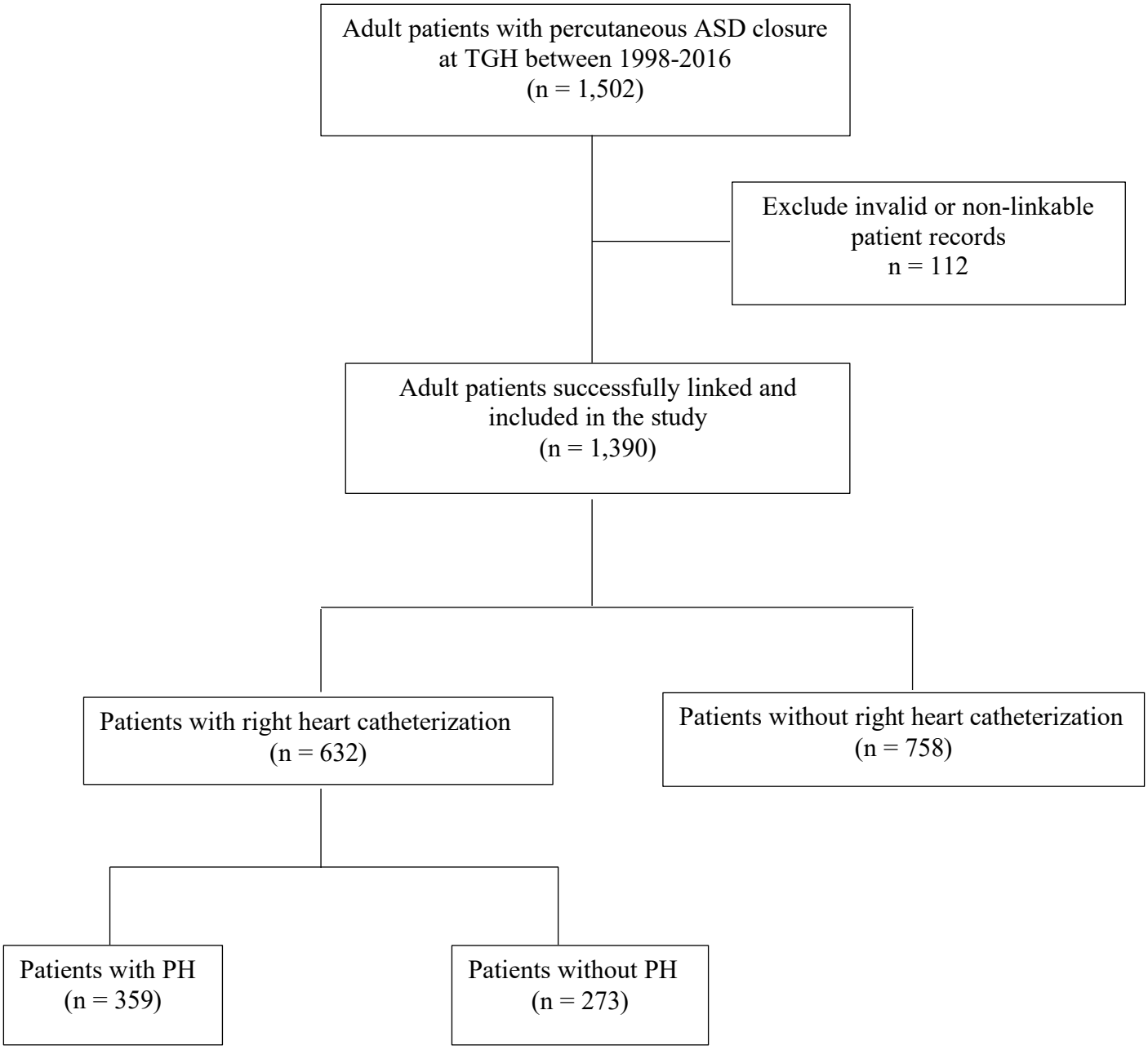
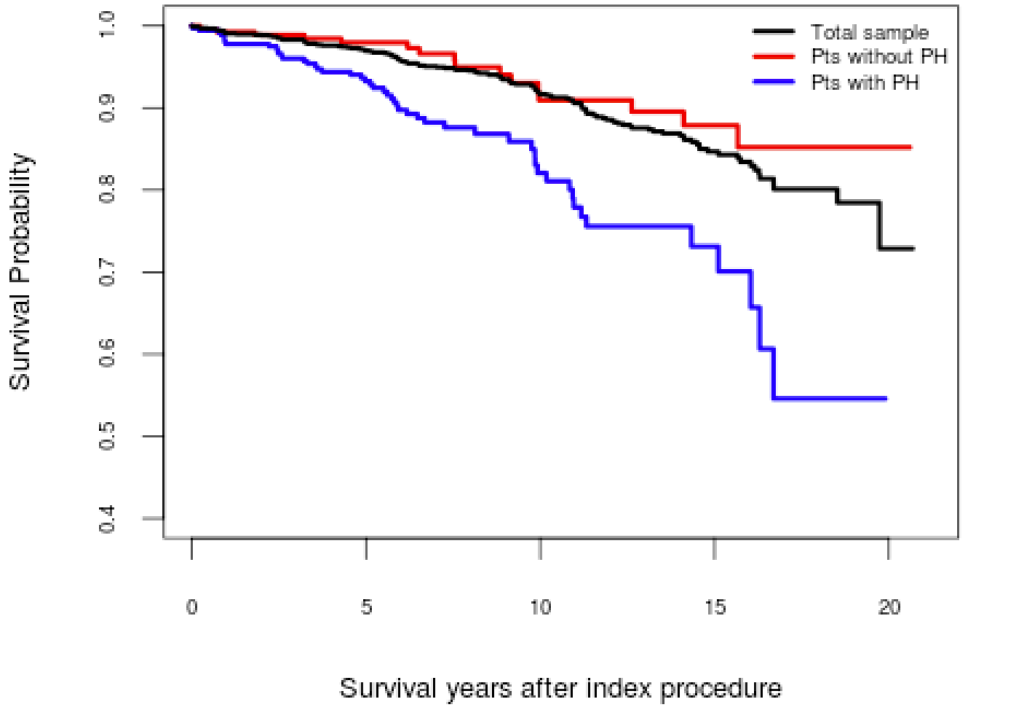


Figure 2. Unadjusted survival from all-cause mortality in patients with and without PH (n = 632)



The p value for log rank test comparing PH and non-PH groups for all-cause survival was <0.001.

3.1.7 Appendices

Appendix A. Codes of clinical variables used for baseline characteristic and long-term follow-up outcomes

Table A1. Baseline variables

	CIHI DAD/NACRS/SDS (Inpatient codes)	OHIP (outpatient codes)
Past myocardial infarction	ICD9 codes: 410 ICD10 codes: I21, I22	
	Rule: 1 DAD code in the past two years.	
Coronary artery disease [1]	ICD9 codes: 410-414 ICD10 codes: ('I20' 'I21' 'I22' 'I23' 'I24' 'I25') CCP codes: 481, 4802, 4803, 4809 CCI codes: 1IJ50, 1IJ57, 1IJ76	410, 412, 413, Z434, G298, R742, R743
	Rule: 1 DAD/NACRS or 2 OHIP codes in the past two years.	
Hypertension	ICD-9 codes: 401, 402, 403 404, 405 ICD-10 codes: I10, I11, I12, I13, I15 OHIP	401, 402, 403 404, or 405
	Rule: 1 DAD/SDS or 1 OHIP claim followed within two years by either an OHIP claim or a DAD claim (1991 to present).	
Atrial fibrillation	ICD9 codes: 4273 ICD10 codes: I480, I4890	427, Z437
	Rule: 1 DAD/NACRS or 4 OHIP claim in 1 year in the past two years.	
Heart failure	ICD-9 code: 428 ICD-10 codes: I500, I501, I509	428
	Rule: one NACRS, DAD, SDS, or OHIP claim and a second claim (from either) in 1 year (1991 to present) or any 1 DAD record	
Stroke	ICD9 codes: 430, 431, 434, 436, 362.3 ICD10 codes: I60, I61, I63 (excluding I63.6), I64, H34.1	
	Rule: 1 DAD code in the past 2 years.	
Diabetes	ICD-9 code: 250 ICD-10 codes: E10, E11, E13, E14	250, Q040, K029, K030, K045, K046
	Rule: two OHIP diagnostic codes or 1 OHIP service code or 1 DAD/SDS code within 2 years (1991 to present)	
Renal failure	ICD9 codes: 585, 586 ICD10 codes: E102, E112, E132, E142, I12, I13, N08, N18, N19	
	Rule: 1 DAD code in the past 2 years.	
COPD	ICD9 codes: 491, 492, 496 ICD10 codes: J41, J42, J43, J44	491, 492, 496
	Rule: three or more OHIP codes and/or one or more DAD code within two years (1991 to present).	
Malignancy	ICD9 codes: 140-208 ICD10 codes: C00-C97	
	Rule: 1 DAD code in the past 2 years.	

*Age, sex, body mass index, echocardiographic variables (tricuspid regurgitation, systolic pulmonary arterial pressure, diastolic pulmonary arterial pressure, mean pulmonary arterial pressure, left atrial mean pressure, right ventricular systolic pressure, right ventricular diastolic pressure, right atrial mean pressure, shunt (Qp:Qs), defect size, and cardiac output), and pulmonary hypertension status were obtained from the ASD clinical registry.
CCI: Canadian Classification of Health Interventions; CCP: Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP); CIHI: Canadian Institute of Health Information; DAD: Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; OHIP: Ontario Health Insurance Plan; SDS: Same Day Surgery.

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Table A2. Outcomes

Outcome	CIHI DAD/NACRS (Inpatient codes)	OHIP (outpatient codes)
Acute myocardial infarction	ICD9 codes: 410 ICD10 codes: I21, I22	
Heart failure*	ICD9 codes: 428 ICD10 codes: I50	428
Stroke	ICD9 codes: 430, 431, 434, 436, 362.3 ICD10 codes: I60, I61, I63 (excluding I63.6), I64, H34.1	
Atrial fibrillation*	ICD9 codes: 4273 ICD10 codes: I480, I4890	427, Z437
New pacemaker	CCI codes: 1HB53, 1HZ53, 1HD54, 1HD53 CCP codes: 49.7, 49.71, 49.72, 49.73, 49.74, 49.84, 49.83	R752
Any open-heart surgery	CCI codes: 1IJ76, 1HS80 (excluding 1HS80GPBD, 1HS80GPFE, 1HS90), 1HU80 (excluding 1HU80GPBD, 1HU80GPBP, 1HU80GPFF, 1HU80GPFE), 1HU90, 1HV80 (excluding 1HV80GPBD, 1HV80GPBP, 1HV80GPFE), 1HV90, 1HT80 (excluding 1HT80GPBD, 1HT80GPBP, 1HT80GPFE), 1HT90, 1HZ85, 1HY85, 1HN80 (excluding 1HN80GPGX and 1HN80GPFL), 1HX86, 1HM78LA, 1HM80LA, 1HM57LA, 1HN71LA, 1HN87LA, 1HP78LA, 1HP80LA, 1HP82,1HP83, 1HP87, 1HR71LA, 1HR80LA, 1HX78, 1HX78, 1HX80,1HX83, 1HR80, 1HR84, 1HR87, 1HX71,1HZ56LA, 1HX87, 1HP53, 1HP55, 1HW78LA, 1HW79LAXXA, 1HW79LAXXL, 1HW79LAXXN, 1HH59LAAD, 1HH59LAAW, 1HH59LAGX, 1HH71LA, 1HH71PN, 1HJ82, 1HZ87, 1HZ57LA, 1HZ53LAFR, 1HZ53LAFS, 1HZ53LAKP, 1HZ53LANK, 1HZ53LANL, 1HZ53LANM, 1HZ53LANN, 1HZ53QANK, 1HZ53QANL, 1HZ53QANM, 1HZ53SYFR, 1HZ53SYFS, 1HZ55LAFS, 1HZ55LAKP, 1HZ55LANK, 1HZ55LANL, 1HZ55LANM, 1HZ56LA, 1HZ57LA, 1HZ70LA, 1HZ80LA, 1HZ80LAXXA, 1HZ80LAXXK, 1HZ80LAXXL, 1HZ80LAXXN, 1HZ80LAXXQ, 1HZ80WKAG, 1HZ87LA, 1HZ87LAXXA, 1HZ87LAXXL, 1HZ87LAXXN, 1HZ87LAXXQ,1LA84, 1LC84 CCP codes: 48.1, 47.26, 47.27, 47.22, 47.23, 47.24, 47.25, 47.28, 47.29, 45.6, 49.5, 47.52, 47.61, 47.6, 47.34, 47.39, 47.35, 47.7, 47.9, 49.1, 49.12, 49.2, 47.8	
Cardiovascular mortality	**Cause of death on death certificate (ORGD database):** ICD9 codes: 390–434, 436–448 ICD10 codes: I00-I79	

*Outcomes were defined as any of the listed codes occurring at least once in inpatient or outpatient billing codes except for heart failure (1 inpatient or 2 outpatient claims [1]) and atrial fibrillation (1 inpatient or 4 outpatient billing in 1 year or cardioversion (Z437) [2])

CCI: Canadian Classification of Health Interventions; CCP: Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP); CIHI: Canadian Institute of Health Information; DAD:

Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; OHIP: Ontario Health Insurance Plan; ORGD: Office of the Registrar General Database.

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Appendix B. Comparisons of baseline characteristics of patients who had right heart catheterization versus those who did not

	Total sample n= 1390	Right heart catheterization		P value
		No n= 758	Yes n= 632	
Male, n (%)	431 (31.0)	228 (30.1)	203 (32.1)	0.447
Age, mean (SD)	47.73 (16.3)	45.26 (14.8)	50.70 (17.5)	<0.001
Year, n (%)				<0.001
1998-2002	237 (17.1)	168 (22.2)	69 (10.9)	
2003-2007	545 (39.2)	417 (55.0)	128 (20.3)	
2008-2012	324 (23.3)	169-173	151-155	
2013-2016	284 (20.4)	<=5*	280-284	
BMI (kg/m^2), mean (SD)	26.51 (5.5)	26.21 (5.3)	26.87 (5.8)	0.026
Shunt (Qp: Qs), mean (SD)†	1.99 (0.7)	2.00 (0.7)	1.98 (0.8)	0.868
Tricuspid regurgitation, n (%)†				
No/mild	762 (78.7)	464 (80.7)	282 (71.8)	<0.001
Moderate/severe	206 (21.3)	111 (19.3)	95 (24.2)	
Hypertension, n (%)	452 (32.5)	198 (26.1)	254 (40.2)	<0.001
Diabetes, n (%)	139 (10.0)	58 (7.7)	81 (12.8)	0.002
COPD, n (%)	132 (9.5)	50 (6.6)	82 (13.0)	<0.001
Coronary artery disease, n (%)	294 (21.2)	118 (15.6)	176 (27.8)	<0.001
Stroke, n (%)	36 (2.6)	19 (2.5)	17 (2.7)	0.964
Atrial fibrillation, n (%)	170 (12.2)	72 (9.5)	98 (15.5)	0.001
Malignancy, n (%)	17 (1.2)	6 (0.8)	11 (1.7)	0.175
Prior MI, n (%)	15 (1.1)	8 (1.1)	7 (1.1)	1
Heart failure, n (%)	38 (2.7)	11 (1.5)	27 (4.3)	0.002
Renal failure, n (%)	4-8	<= 5*	4-8	NA
CCI ≥1, n (%)	184 (13.2)	77 (10.2)	107 (16.9)	<0.001

BMI: body mass index; CCI: Charlson comorbidity index; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; SD: standard deviation

**Small cells (≤5 observations) suppressed.*

†Data on Qp:Qs was missing in 1091 (78.5%) patients (646 versus.445, no RHC versus RHC), tricuspid regurgitation was missing in 422 (30.4%) patients (183 versus. 239, no RHC versus. RHC). All calculations with these variables were completed after excluding the missing values.

Appendix C. Baseline invasive (RHC) and echocardiographic parameters in patients with right heart catherization

	Total sample[†]	Pulmonary hypertension		P value
		No	Yes	
PA systolic pressure (mmHg), mean (SD)	35.83 (12.36)	25.88 (5.26)	43.40 (10.73)	<0.001
PA diastolic pressure (mmHg), mean (SD)	14.10 (5.69)	9.81 (3.04)	17.27 (5.08)	<0.001
PA mean pressure (mmHg), mean (SD)	22.69 (7.54)	16.14 (3.07)	27.66 (5.96)	<0.001
LA mean pressure (mmHg), mean (SD)	10.72 (4.52)	8.70 (3.33)	12.16 (4.70)	<0.001
RV systolic pressure (mmHg), mean (SD)	35.59 (13.34)	30.85 (8.56)	39.23 (15.12)	<0.001
RV diastolic pressure (mmHg), mean (SD)	4.14 (3.94)	2.77 (3.06)	5.06 (4.19)	<0.001
RA mean pressure (mmHg), mean (SD)	8.63 (4.27)	6.51 (3.14)	10.19 (4.32)	<0.001
Shunt (Qp:Qs), mean(SD)	1.98 (0.77)	1.72 (0.54)	2.19 (0.86)	<0.001
Defect size (mm), mean (SD)[*†]	23.43 (6.95)	22.39 (6.94)	24.22 (6.86)	0.001
Cardiac output L/min (Fick), mean (SD)	4.83 (1.77)	4.94 (1.67)	4.75 (1.83)	0.258

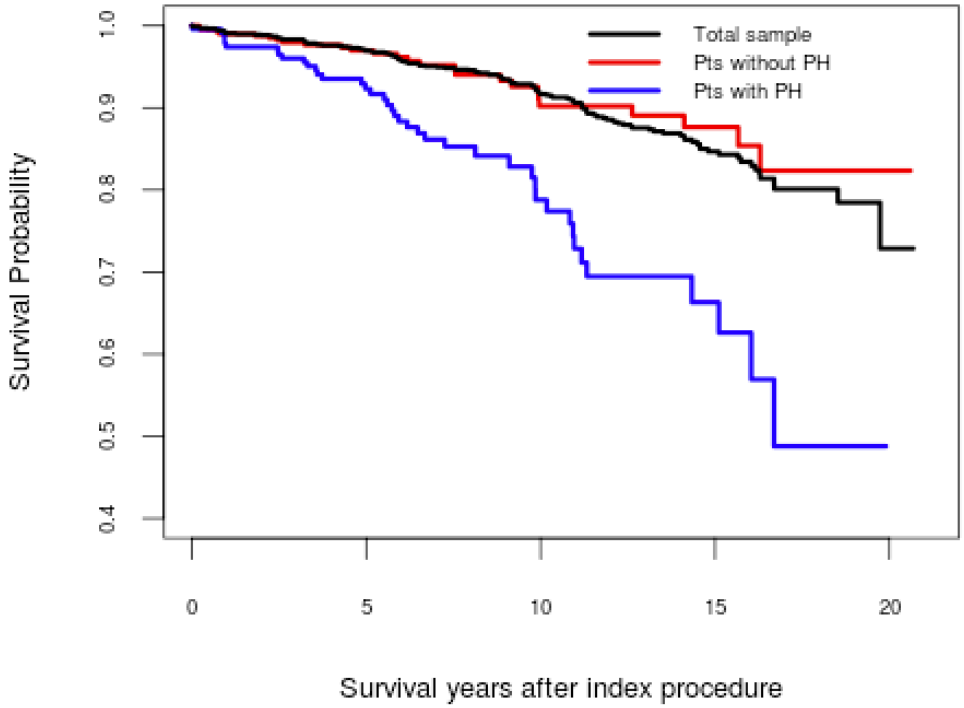
LA, left atrium; mm, millimeters; mmHg, millimeters of mercury; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SD, standard deviation.

Size of first defect.

[†]Data was missing on PA systolic pressure in 7 (1.1%) patients, PA diastolic pressure in 21 (3.2%) patients, LA mean pressure in 173 (27.4%) patients, RV systolic pressure in 243 (38.4%) patients, RV diastolic pressure in 134 (21.2%) patients, RA mean pressure in 42 (6.6%) patients, shunt in 445 (70.4%) patients, defect size in 2 (0.31%) patients, cardiac output l/min (Fick) in 172 (27.2%) patients. All calculations with these variables were completed after excluding the missing values.

Appendix D. Sensitivity analysis using the prior PH cut-off (mPAP ≥ 25 mmHg)

Figure D. Unadjusted Kaplan-Meier survival curves for all-cause mortality



The p value for log rank test comparing PH and non-PH groups for all-cause survival was <0.001

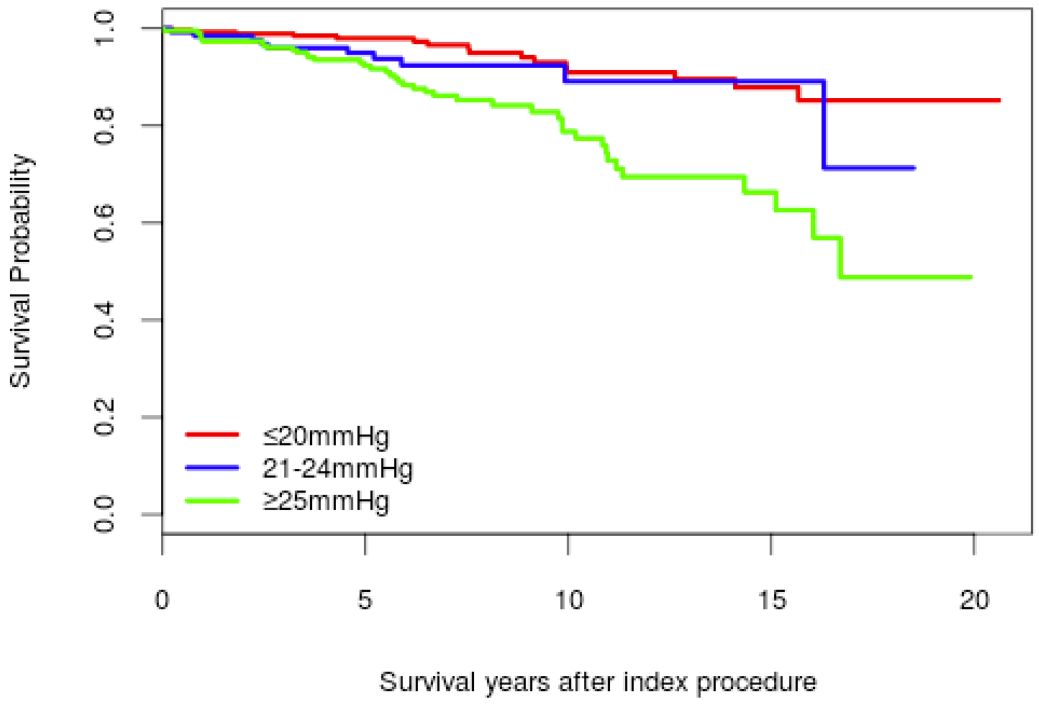
Table D. Cox proportional hazard models for adverse outcomes†, n = 632 (n = 231 patients with PH based on old cut off)

	Unadjusted HR (95% CI)	P value	Adjusted Model 1 HR (95% CI)	P value	Adjusted Model 2 HR (95% CI)	P value
New onset AF	2.72 (1.77; 4.20)	<0.001	1.86 (1.18; 2.93)	**0.007**	1.73 (1.09; 2.75)	**0.021**
MACCE	3.63 (2.35; 5,59)	<0.001	2.06 (1.31; 3.25)	**<0.001**	1.89 (1.18; 3.02)	**0.013**
All-cause mortality	3.01 (1.84; 4.94)	<0.001	1.55 (0.92; 2.58)	**0.031**	1.53 (1.18; 2.55)	**0.050**

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular event.
MACCE defined as heart failure, stroke, myocardial infarction, or CV mortality
Model 1: adjusted for age for all outcomes.
Model 2 adjusted for age, hypertension, diabetes, and COPD, and atrial fibrillation for MACCE and all-cause mortality and adjusted for age, hypertension, diabetes and COPD for new onset AF outcome.
†Patients without PH used as reference population.

Appendix E. Comparison of all-cause mortality by mPAP category

Figure E. Unadjusted Kaplan-Meier survival curves for all-cause mortality by mPAP category



The p value for log rank test comparing 21-24mmHg to ≥ 25mmHg for all-cause survival was <0.001

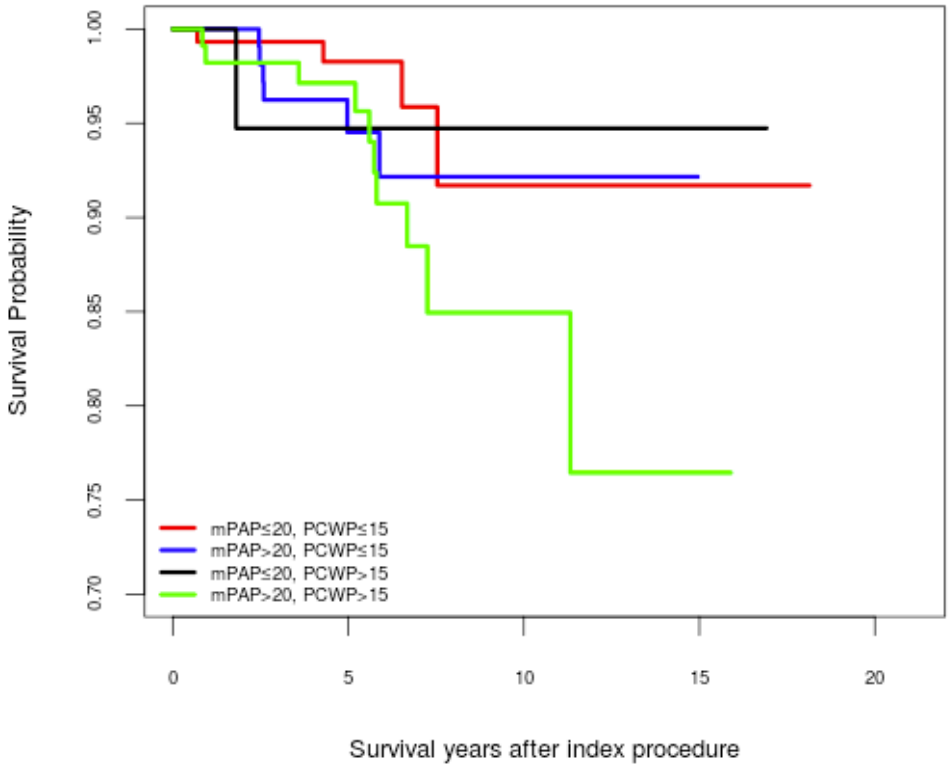
Table E. Cox proportional hazards models for patients by mPAP category for all-cause mortality (n = 632)

mPAP (mmHg)	n	Unadjusted HR (95% CI)	P value	Adjusted Model 1 HR (95% CI)	P value	Adjusted Model 2 HR (95% CI)	P value
≤20†	273	1.00		1.00		1.00	
21-24	128	1.71 (0.77; 3.78)	0.186	0.82 (0.36; 1.83)	0.621	0.79 (0.35; 1.80)	0.563
≥25	231	3.60 (2.01; 6.43)	<0.001	1.41 (0.76; 2.61)	0.271	1.31 (0.71; 2.45)	0.391

CI: confidence interval; HR: hazard ratio; mPAP: mean pulmonary artery pressure.
Model 1: adjusted for age.
Model 2: adjusted for age, hypertension, diabetes, COPD, and atrial fibrillation.
†*Patients with mPAP ≤ 20 were used as reference population.*

Appendix F. Comparison of all-cause mortality by PH category

Figure F. Unadjusted Kaplan-Meier survival curves for all-cause mortality by PH category



The p value for log rank test comparing all groups to mPAP ≤20 & PCWP ≤15 for all-cause survival was 0.3

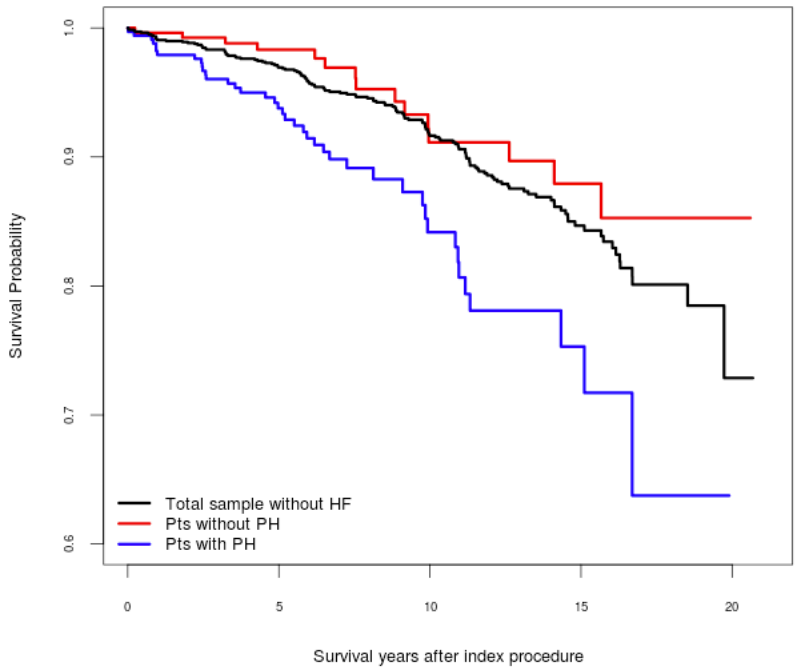
Table F. Cox proportional hazards models for all-cause mortality by PH category (n=395)

	n	Unadjusted HR (95% CI)	P value	Adjusted Model 1 HR (95% CI)	P value	Adjusted Model 2 HR (95% CI)	P value
mPAP ≤20 & PCWP ≤15†	**149**	**1.00**		**1.00**		**1.00**	
mPAP >20 & PCWP ≤15	114	1.99 (0.56, 7.92)	0.284	0.74 (0.20, 2.79)	0.661	0.88 (0.24, 3.20)	0.842
mPAP ≤20 & PCWP >15	20	1.76 (0.20, 15.82)	0.612	1.77 (0.20, 15.99)	0.609	2.53 (0.26, 24.39)	0.421
mPAP >20 & PCWP >15	112	2.83 (0.89, 9.02)	0.079	0.62 (0.17, 2.27)	0.470	0.53 (0.15, 1.92)	0.331

CI: confidence interval; HR: hazard ratio; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure.
Model 1: adjusted for age.
Model 2: adjusted for age, hypertension, diabetes, COPD, and atrial fibrillation.
†Patients with mPAP ≤20 and PCWP ≤15 were used as reference population.

Appendix G. Comparison of all-cause mortality in patients without HF

Figure G. Unadjusted Kaplan-Meier survival curves for all-cause mortality in patients without HF (n = 605)



The p value for log rank test comparing patients without HF and without PH, to patients without HF with PH for all-cause survival was <0.01

Table G. Cox proportional hazards models for all-cause mortality patients without HF (n = 605)

	Unadjusted HR (95% CI)	P value	Adjusted Model 1 HR (95% CI)	P value	Adjusted Model 2 HR (95% CI)	P value
mPAP ≤20†	**1.00**		**1.00**		**1.00**	
mPAP >20	2.65 (1.46, 4.82)	<0.001	1.04 (0.56, 1.96)	0.892	0.99 (0.53, 1.89)	0.999

CI: confidence interval; HF: heart failure; HR: hazard ratio; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure.
Model 1: adjusted for age.
Model 2: adjusted for age, hypertension, diabetes, COPD, and atrial fibrillation.
†Patients with no HF and mPAP ≤ 20 were used as reference population.

Appendix H. Studies reporting a comparison between patients with and without PH undergoing percutaneous ASD closure

Author, year	ASD cohort years	Sample characteristics	PH measurement	Follow up duration	Baseline and outcome comparisons: PH vs non-PH
Yong et al., 2009 (81)	1999 to 2006	• n = 216 • mean age at closure 53.9 (15.7) • single center	TTE	Median follow-up of 1.25 (range, 0.66 to 3.6) years	• Defined PH as mPAP ⩾ 25 mmHg • Only compared baseline characteristics between PH non-PH groups • Patients with PH were older and had more comorbidities at baseline including coronary artery disease, atrial arrhythmia, and NYHA class ⩾ 3 compared to patients without PH • No outcome analysis
Ranard et al., 2019 (124)	2000 to 2011	• n = 228 • mean age at closure 49.1 (16.2) • single center	RHC	Mean follow-up time of 7.4 (3.3) years	• Defined PH as mPAP ⩾ 25 mmHg • PH was present in 48 of 228 patients (21.1%) and was more common in older patients defined as > 48 years (median age of the cohort) (31.3% versus 10.6%) • Patients with PH were older and had more comorbidities at baseline including higher BMI and hypertension compared to patients without PH • Older patients with PH had more medical comorbidities including diabetes, hyperlipidemia, and systemic hypertension compared with younger patients with PH. • PH did not impact survival in patients ≤48 years, but PH was associated with fivefold increased risk of death in patients >48 years ($p < 0.01$) in an unadjusted cumulative hazard model.
Present study	1998 to 2016	• n = 632 • mean age at closure 50.7 (17.5) • single center	RHC	Mean follow-up 7.66 (4.65) years	• Define PH as mPAP > 20 mmHg • PH was present in 359 of 632 patients (56.8%) and patients with PH had a higher mean age (56.1 versus 43.1) compared to patients without PH • Patients with PH were older and had more comorbidities at baseline including hypertension, diabetes, COPD, AF, and HF.

					• Based on multivariable Cox proportional hazards models: the HR for all-cause mortality was not significant; HR for MACCE = 2.45, 95%CI=1.38, 4.37 • Sensitivity analysis for old mPAP cut off and by PH severity conducted.

AF: atrial fibrillation, CI: confidence interval, COPD: chronic obstructive pulmonary disease, HF: heart failure, HR: hazard ratio, MACCE: major adverse cardiac and cerebrovascular event, mPAP: mean pulmonary artery pressure, NYHA: New York Heart Association, PH: pulmonary hypertension.

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