Pulmonary Artery Systolic Pressure on Echocardiogram: Filling the Gap in Current Guidelines

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Summary:

A growing number of studies have demonstrated the risk associated with mild elevations in pulmonary artery (PA) pressure as estimated by echocardiography. On right heart catherization in healthy individuals, the average PA systolic pressure is 21 ± 4 mm Hg; on echocardiography, estimated PA systolic pressure of >30 mm Hg is outside the normal range in most healthy individuals. Elevated PA systolic pressure is present in 40% of all echocardiograms performed clinically and is associated with a five-year mortality of 25-40%. However, current guidelines do not sufficiently highlight risk and risk-reduction approaches for the sizable patient population with elevated pulmonary artery pressures but do not have underlying severe pulmonary vascular disease such as pulmonary arterial hypertension. Increased awareness of this frequently reported high-risk echocardiographic finding, and multi-disciplinary risk-reduction approaches for patients

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Search Strategy:

For Healthy Subjects studies:

Search: (pulmonary artery systolic pressure) AND (echocardiography) AND (healthy): 124 results

Search: (pulmonary artery catheter) OR (right heart catheter) AND (healthy) from 2008 – 2020 (i.e. since Kovacs review in 2009): 155 results

Healthy subjects were as defined in the individual studies but generally excluded persons with known or suspected cardiopulmonary diseases

For Community studies:

(echocardiography) AND (pulmonary artery pressure) AND (community)

(echocardiography) AND (pulmonary artery pressure) AND (population-based)

(echocardiography) AND (pulmonary artery pressure) AND (cross-sectional)

(echocardiography) AND (pulmonary artery pressure) AND (general population)

(echocardiography) AND (pulmonary artery pressure) AND (prospective longitudinal)

Community studies included persons recruited from particular community settings as noted, who may or may not have cardiopulmonary or other diseases prevalent in the given community.

References were reviewed and other studies known to the authors were also included.

Studies included in systematic reviews were not reduplicated.

with metabolic and cardiopulmonary comorbidities and elevated pulmonary artery pressures, are urgently needed.

Pulmonary hypertension is a common and highly morbid condition associated with decreased survival. Defined as mean pulmonary artery pressure > 20 mm Hg measured by right heart catherization[1], based on the upper limit of normal pulmonary artery pressure in healthy individuals at rest and increased risk associated with mPAP >20 mmHg, it is present in more than three-quarters of all right heart catheterizations performed[2,3]. However, the pulmonary artery systolic pressure can also be estimated (ePASP) noninvasively with adequate reliability by measuring the velocity of the tricuspid regurgitation (TR) jet using echocardiography. ePASP is estimated by calculating Doppler estimated transtricuspid gradient (TR gradient= 4 x (TR velocity)^2) and adding estimated right atrial pressure to it based on the size of the inferior vena cava and collapsibility with sniff [4]. Indeed, ePASP is a standard assessment in contemporary echocardiography, and can be measured in about two-thirds of all echocardiograms[5,6]. Tables 1 and 2 delineate values of ePASP, measured by echocardiography or right heart catheterization, in healthy volunteers and community-based cohorts, respectively. On right heart catherization performed in healthy individuals, the average PASP is 21 ± 4 mm Hg, with an upper limit around 30 mm Hg [7]. From echocardiography performed in healthy individuals, the average ePASP is similar to measurements from right heart catheterization, generally in the teens to low-20s mm Hg range on average; ePASP above 30 mm Hg is uncommon, with the exception of young well-trained athletes, high-altitude residents, and the elderly. Notably, ePASP of >30 mm Hg is below the traditional threshold of 40 mm Hg typically cited as concerning for possible PH and actually relates more closely to a mean PA pressure   20 mm Hg.[8,9] Mean PA pressure in this range (mPAP 20-24 mm Hg) associates independently with increased mortality[2], suggesting that ePASP levels <40 mmHg are informative for identifying at-risk patients as well. While an elevated ePASP is a risk marker, absence of a TR jet notably does not rule out elevated pulmonary artery pressure [10]. Therefore, in the minority of patients without a measureable ePASP, clinical suspicion of elevated ePASP based on short pulmonary acceleration time on echocardiography, notching in the Doppler flow recording in the right ventricular outflow track, and presence of right ventricular hypertrophy, dilation or dysfunction may be helpful in identifying at-risk patients [10,11].

Elevated ePASP > 30 mm Hg is present in over 40% of clinical echocardiograms performed[12,13] and in 25% of the adult population on echocardiograms performed in population-based samples[5,6]. Strikingly, mortality risk rises substantially with an ePASP > 30 mm Hg, confirming the narrow upper bound of the healthy range of pulmonary artery pressures. Five-year mortality in patients with an ePASP of 30-32 mm Hg on clinical echocardiograms is 28·9%, 66% higher than those with a PASP 28-30 mm Hg and 2·5-fold higher than those with an ePASP < 22 mm Hg[13]. One-year mortality in patients with an ePASP of 30-32 mm Hg is 10·1% [13]. In studies conducted in the general population, the risk of mortality rises by about 40% with every 10 mm Hg increase in the PA systolic pressure[14] and is notably higher with ePASP   28 mm Hg compared to those with lower ePASP[5]. This results in a 9-10% percent eight-year mortality in the general population with an ePASP of 30-32 mm Hg[5], and a 25% ten-year mortality with ePASP   40 mm Hg[14] . The poor

prognosis associated with elevated ePASP on echo is similar to that associated with mean PA pressure on right heart catheterization, where the five-year mortality is about 25% in patients with mean PA pressure between 19-24 mm Hg, and about 40% in patients with mean PA pressure >25 mm Hg[2] (Figure 1). Similar to systemic blood pressure, PASP increases with age, related to increased stiffness of the pulmonary vasculature[5]. While PASP has a modest and significant corelation with age (r value: 0.19-0.48) [5,15-19], elevated PASP cannot be considered benign since, even after adjustment for age, an elevated PASP remains associated with poor outcomes [5,6]. Therefore, based on available data, a resting mean PA pressure < 20mmHg or PA systolic pressure < 30mmHg appear to be a healthy (or optimal) pressure in the pulmonary circulation and elevation in ePASP is a common and high-risk finding on echocardiogram.

In the contemporary PH guidelines, in symptomatic patients, tricuspid regurgitant velocity measured on echocardiogram, along with other clinical characteristics (Figure 2), plays an important role in the algorithm targeted towards identification of (Group 1 PH) pulmonary arterial hypertension (PAH) and (Group 4) chronic thromboembolic pulmonary hypertension (CTEPH), the two groups of PH patients for which there are well-proven therapeutic interventions.[4] While this diagnostic strategy is focused on identifying patients with PAH and CTEPH, a significant gap in recommendations exists for the management of patients with elevated ePASP who do not fall into these distinct diagnostic groups. This is particularly true of symptomatic patients with mildly to moderately elevated ePASP on echocardiogram (PASP 30-50 mm Hg) without clear risk factors or conditions associated with PAH or CTEPH and with obesity, metabolic, and cardiopulmonary co-morbidities. Therefore, patients with mildly elevated ePASP are often continued on non-PH focused management without a thorough consideration of the implication of this high-risk feature. The reasons for the missed opportunity to mitigate risk more aggressively in these vulnerable patients are likely lack of recognition of the poor prognosis associated with even mildly elevated PASP and an absence of well-defined strategies to manage these patients and improve outcomes.

A consideration of the pathophysiological basis for the poor outcomes associated with elevated PA pressures can inform the development of appropriate strategies for risk reduction. In select groups of PH patients, such as those with PAH and Group 4 PH, elevation of PA pressure is primarily caused by underlying pulmonary vascular disease with a clear pathophysiological link between the primary disease and consequent morbidity and mortality. Not surprisingly, these patients benefit from pulmonary vasoactive medications and other interventions specifically aimed at the underlying pulmonary vascular disease. However, since these conditions are rare, in the vast majority of individuals, elevated PA pressures are likely a consequence of increased left atrial pressure, increase in PA stiffness, and pulmonary vascular remodeling and impaired vasoreactivity in the setting of cardiopulmonary and metabolic disorders, perhaps acting in combination in any given patient. As demonstrated by Wolsk et. al. fluid infusion resulting in an acute increase in pulmonary capillary wedge pressure, a surrogate for left atrial pressure, can increase PASP even in healthy individuals [19]. About 22% and 78% of patients have elevated pulmonary capillary wedge pressures (>15 mm Hg) in settings of mean PAP 19-24 mm Hg and mean PAP >25 mm Hg, respectively[2,3]. Therefore, increased left atrial

pressure, frequently resulting from LV diastolic dysfunction that is known to be associated with cardiopulmonary and metabolic diseases, is an important reason for elevated PA pressure. Increasing age also corelates with elevations in PA systolic pressure due to pathophysiological mechanisms such as an increased incidence of diastolic dysfunction and increase in PA stiffness. Age, gender, cardiopulmonary and metabolic comorbidities have been independently associated with increased prevalence of elevated ePASP[6], and it is common to have multiple cardiopulmonary comorbidities present in the same patient. Yet, at the same time, elevated PA pressure is associated with poor outcomes independent of age and co-morbidities[14]. These contrasting observations can be reconciled if we consider elevation of PA pressure as both a risk marker on its own and as a risk modifier in the presence of co-morbidities, wherein an elevation of pulmonary vascular resistance with consequent right heart dysfunction adds to the burden of the primary disease (Figure 3). Indeed, even mildly elevated PA pressures are associated with evidence of right ventricular dysfunction that is associated with poor outcomes in the presence or absence of comorbid conditions[12].

PH guidelines already provide algorithms for appropriate and timely referral to specialized PH centers for patients with severe pulmonary vascular disease. However, due to differences in the underlying pathophysiology outlined above, the majority of patients with elevated PASP will not benefit from pulmonary vasoactive medications but will require more multidimensional management strategies. While echocardiographic ePASP measurement has moderate precision compared to right heart catheterization [20], an elevated ePASP serves as a marker to identify a population of patients in need of careful clinical assessment and more intensive risk factor modification. We believe that it is time to develop risk-reduction programs for patients with elevated PASP that will be widely applicable to these at-risk patients and that need not be confined to PH centers. Disease management and risk-reduction approaches are commonly used in other high-risk conditions, such as preventive cardiology clinics for coronary artery disease management and metabolic clinics for diabetes. Accumulating evidence has already identified risk factors for elevated ePASP (Figure 3); these include comorbidities with well-defined management approaches but which cross multiple specialties (cardiology, pulmonary, endocrine), resulting in fragmentation of care and lost opportunities for an integrative approach to management.

There is a strong rationale to evaluate and aggressively manage patients with elevated PA pressures using the key principles outlined in Figure 4. One model for care in these patients is a multidisciplinary PH clinic to evaluate patients with elevated ePASP and, in those without identifiable underlying severe pulmonary vascular disease, manage their cardiopulmonary and metabolic risk factors in a coordinated manner. Experience with such a clinic at a non-tertiary care hospital has shown that an appropriate PH work-up can be completed in the majority of patients, and the most common interventions, such as optimizing diuretic doses for volume overload and optimizing oxygen requirements and treatment for sleep disordered breathing,[21] may be associated with reduced hospitalizations in this population. Such a strategy may also reduce the inappropriate use of pulmonary vasodilator medications in those patients with elevated PA pressures lacking a clear indication for their use, such as those with group 2 pulmonary hypertension. These clinics could also serve as platforms for registries and clinical trials that could be developed to

accumulate evidence in support of specific risk reduction approaches for elevated PASP. This model would allow for better capture of the sizeable population of at-risk patients that are overlooked at present[22]. It may also afford the opportunity for both earlier diagnosis of patients with pulmonary vascular disease and, through early intervention and risk factor management, the prevention of progression of mildly elevated pulmonary artery pressures to severe PH.

In summary, current data shows that patients with a PASP > 30 mm Hg are at risk for increased morbidity and mortality, which may potentially relate to underlying multimorbidity, the elevated pressure within the pulmonary circulation itself, and its consequent effects on the heart. While we do not advocate for screening general population for elevated PASP, this is a common high-risk finding on clinical echocardiograms that often receives inadequate attention. Clinicians should be aware of the adverse prognosis associated with elevated PASP, identify those with suspected group 1 and group 4 PH for specialty referral, and address treatable and/or modifiable factors such as manifest volume overload, systemic hypertension, hypoxia, diabetes, obesity, and obstructive sleep apnea in those who are not appropriate for referral. Given the complexity of this evaluation and management strategy, a multidisciplinary approach to evaluate and manage these patients would, however, be ideal. Finally, there is a crucial need for more data to improve our understanding of the problem of elevated PASP at a population level and to determine the most appropriate screening and risk-reduction strategies.

Acknowledgements:

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Key Message:

- Estimated pulmonary artery systolic pressure (ePASP) > 30 mm Hg is outside the normal range and is reported in about 40% of clinically indicated echocardiograms

- Elevated ePASP is associated with 25-40% 5-year mortality and is frequently associated with cardiopulmonary and metabolic co-morbidities

- Current pulmonary hypertension (PH) guidelines outline assessment and referral approaches to identify Group 1 and Group 4 PH, which are relatively rare diseases, but management of the large number of patients with elevated ePASP associated with cardiopulmonary and metabolic co-morbidities is not well addressed.

- We propose an approach of thorough multidisciplinary assessment and aggressive risk factor management to mitigate risk in this high-risk population.
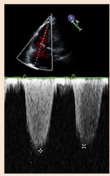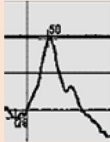
Figure 1:
Prevalence and prognosis of elevated pulmonary artery pressures by echocardiograms performed in either community based[5,6] or referral[13] population and right heart catheterizations performed in referral populations[2,3]. The echocardiograms and right heart catheterizations in the referral populations were clinically indicated. The mortality rates are unadjusted for age or co-morbidities. PASP: Pulmonary Artery Systolic Pressure; mPAP: Mean Pulmonary Artery Pressure; y: year

SYMPTOMATIC PATIENTS:

Echocardiographic probability of PH	TR Jet (m/s)	ePASP (mm Hg)	Echo PH Signs#	Risk Factors for PAH/CTEPH	Recommendation	Class	LOE
Low	<2.8	<36	-	-	Alternative diagnosis should be considered	IIa	C
	<2.8	<36	-	+	Echo follow-up should be considered	IIa	C
Intermediate	<2.8	<36	+	-	Alternative diagnosis, echo follow-up, should be considered, Further investigation of PH may be considered*	IIa	C
	<2.8	<36	+	+	Further assessment of PH including RHC should be considerede	IIa	B
	2.9-3.4	39-51	-	-	Alternative diagnosis, echo follow-up, should be considered, Further investigation of PH may be considered*	IIa	C
	2.9-3.4	39-51	-	+	Further assessment of PH including RHC should be considerede	IIa	B
High	2.9-3.4	39-51	+	-	Further investigation of PH (including RHC*) is recommended	I	C
	2.9-3.4	39-51	+	+	Further investigation of PH* including RHC is recommended	I	C
	>3.4	>51	+ or -	-	Further investigation of PH (including RHC*) is recommended	I	C
	>3.4	>51	+ or -	+	Further investigation of PH* including RHC is recommended	I	C

ePASP assumes RA pressure of 5 mm Hg
*Depending on the presence of risk factors for PH group 2, 3 or 5.
#Characteristics of RV, PA flow, IVC and RA

Figure 2:

Summation of the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines on suggested assessment and management of symptomatic patients with suspected pulmonary hypertension defined as mean PA pressure 25mmHg. Figure adapted from Table 8A and 9 of the 2015 ESC/ERS guidelines.[4]

Elevated PA pressure with Cardiopulmonary and Metabolic Comorbidities:

Cardiopulmonary/ Metabolic Comorbidities

↑ Left atrial pressure, ↑ PA stiffness, hypoxia, mild pulmonary vascular remodeling and impaired vasoreactivity

Factors associated with elevated PA systolic Pressure:
Age
Female Sex
Obesity
Systemic pulse pressure
Diabetes
Severe Aortic and Mitral valve Disease
Chronic Lung Disease
Heart Failure

Biomarker/ Risk Marker

Substrate/ Susceptibility

Excessive remodeling → RV Dysfunction
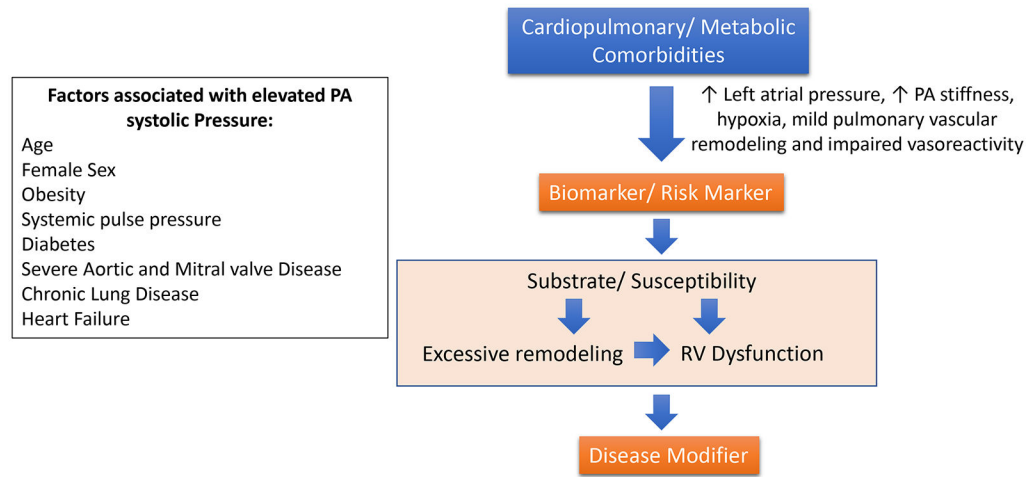
Disease Modifier

Figure 3:
Relationship of comorbidities and risk factors with elevated pulmonary artery systolic pressure. In the context of a patient with cardiopulmonary and metabolic comorbidities, elevated pulmonary artery systolic pressure may serve as both a biomarker and disease modifying factor.

Principles for Management of Patients with Elevated PA Systolic Pressure

- Assessment of volume status and diuresis
- Assessment of oxygenation: Daytime, Exercise and during Sleep
- Management of Obesity
- Management of diabetes and metabolic syndrome
- Systemic hypertension control
- Mitral and Aortic valvular disease evaluation and management
- Exercise/ Physical Activity
- Referral to PH expert center based on current guidelines

Figure 4:
Principles for management of patients with elevated pulmonary artery (PA) systolic pressure based on potentially modifiable pathophysiologic factors

Table 1:

Values and upper limits of pulmonary artery systolic pressure in selected large cohort studies of echocardiography and right heart catheterization in healthy subjects

Authors	Population	n	Age (Mean ± SD or median (IQR)) Sex (%Female)	Modality	Mean or median PASP or RVSP in mmHg (SD or IQR):	Upper limits, Pulmonary Artery Systolic Pressure
D'Andrea A et al (2011)[15]	Healthy control subjects and Highly-trained athletes including endurance- and strength-trained athletes	Healthy Controls n=230, Athletes n=615: Endurance-trained athletes n =370, Strength-trained n=245	Healthy controls: 27·5 ± 11.3 years (yrs), 39.1% female, Athletes:28·4 ± 10.1 yrs, 36·7% female	Echocardiogram	Healthy controls: 17·6 ± 4.6 *; Athletes: Endurance-trained: 26·1 ± 6.6 **; Strength-trained: 19·4 (8.1) **	26·8 mm Hg (healthy controls)
D'Andrea et al (2020)[23]	Healthy controls and Endurance athletes	Healthy Controls n=150, Endurance athletes n=350	Healthy controls: 32·4 ± 15·1 yrs, 42·6% female, 31·6 ± 4·2 yrs, 41·5% female	Echocardiogram	Healthy controls: 21·6 ± 3·1 *; Endurance athletes: 25·5 ± 5·8 *	28mmHg (healthy controls)
Ferrara F et al (2016)[17]	Healthy volunteers and those undergoing work assessment without evidence of cardiovascular disease, diabetes, obesity, significant valvular disease	n=1168	45·1 ± 16 yrs 52.5% female	Echocardiogram	20.9 ± 5.9 *	Age <40 yrs: 31 mm Hg; Age 40-49 yrs: 32 mm Hg; Age 50-59 yrs: 33 mm Hg; Age 60 yrs: 35.6 mm Hg
Soria R et al (2016)[24]	Systematic review and meta-analysis of echocardiography data on healthy low-altitude and high-altitude study participants from general population	Low-altitude dwellers: n=620, High-altitude dwellers: n=786	Low-altitude: Mean age range: 8.8 – 45yrs, 43·3% female (2·9% sex not recorded); High-altitude: Mean age range: 9·5 – 48 yrs, 38·5% female	Echocardiogram	Low-altitude: 18·4 (95% CI 17·1-19·7); High-altitude: 25·3 (95% CI 24·0 – 26·7)	Low-altitude: 26mmHg High altitude: 36 mm Hg
Yang Y et al (2020)[25]	Healthy male volunteers	n=121	20 (19, 21) 0% female	Echocardiogram	At low altitude: 24·2 ** (20·4, 27·3)	NA
Kovacs G et al (2009)[7]	Systematic review of right heart catheterization data on healthy individuals	n=1187	N/a, 18·9% female, 20·6% sex notrecorded	Right heart catheterization	20·8 ± 4.4	29–6 mm Hg
Wolsk E et al (2019)[19]	Healthy subjects aged 20-80 years from the community (n=60)	n=60	50 ± 17 yrs 53.3% female	Right heart catheterization	21 ± 5	31 mm Hg

IQR: Interquartile range; PASP: Pulmonary artery systolic pressure; RVSP: Right ventricular systolic pressure; SD: standard deviation; Yrs: Years

*
RA pressure based on inferior vena cava (IVC) measurements.

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**Assuming a right atrial (RA) pressure of 5mmHg

Table 2:

Values of pulmonary artery systolic pressure and prevalence and prognosis of elevated pulmonary artery systolic pressure in selected large cohort studies of echocardiography and right heart catheterization in community-based populations

Authors	Population	n	Age (Mean ± SD or median (IQR)) Sex (%Female)	Modality	Mean or median PASP or RVSP in mmHg (SD or IQR):	Prevalence of elevated PASP and prognosis
Brittain E et al (2017)[26]	Middle-aged, community-based biracial study cohort with measurable TR jet	n=1311	51 (47, 53) yrs 49% female	Echocardiogram	31 mm Hg (27, 34) * (median 26mmHg assuming RAP 5mm Hg)	50·0% PASP 31 mm Hg 6·6% PASP > 40 mm Hg
Brittain E et al (2018)[27]	HIV-infected and HIV-uninfected Veterans (matched 1:2) enrolled on or after April 1st, 2003 in prospective longitudinal study with PASP measured on echocardiogram	HIV-infected n=2,831 HIV-uninfected n=5,465	HIV-infected, no PH: 56 yrs, 2.7% female HIV-infected, PH: 57 years, 1.9% female HIV-uninfected, no PH: 57 yrs, 3.8% female HIV-uninfected, no PH: 58 years, 1.1% female	Echocardiogram	36 ± 15 mm Hg (HIV-infected) 36 ± 14 mm Hg (HIV-uninfected)	28% (HIV-infected) and 27% (HIV-uninfected) PASP > 40 mm Hg Adjusted hazard of mortality 40% higher for PASP 30 mm Hg compared to PASP 15 mm Hg (HIV-infected) Adjusted hazard of mortality 21% higher for PASP 30 mm Hg compared to PASP 15 mm Hg (HIV-uninfected)
Choudhary G et al (2013)[6]	Community-based, African-American	n=3,282	56·1 ± 12.6 yrs 67·5% female	Echocardiogram	27 (18, 36) **	35% PASP > 30 mm Hg 6.8% PASP 40 mm Hg
Lam CS et al (2009)[5]	Community-based, white	n=1413 778 without cardiopulmonary disease	63 ± 11 yrs 57% female	Echocardiogram	26 (24, 30) **	25% >30mmHg Adjusted hazard ratio for mortality 1·46 (overall study population) and 2·74 (subpopulation without cardiopulmonary disease) per 10 mm Hg increase in PASP
Leibowitz D et al (2014)[28]	Randomly selected subjects 85 year-old subjects	n=300 with measurable TR jet	85 yrs. 42% female	Echocardiogram	30·5 ± 9.4 (Median 28·3: IQR 24, 34·9)	25% PASP 35 mm Hg Five-year survival significantly worse for PASP > 30 mm Hg
Moreira EM et al (2015)[29]	Sub-study embedded in a population-based prospective cohort study of middle-aged and older adults	n=2,823	76·4 ± 6.2 yrs 59% female	Echocardiogram	26·3 ± 7·0 † (Median 25·3)	≈25% PASP > 30 mm Hg
Teramoto K et al (2020)[30]	Adults > 65 years Older free of Prevalent heart failure and with measurable tricuspid regurgitation participating in community-based prospective longitudinal study	n=2,810	76·2 ± 5.2 yrs 66% female	Echocardiogram	28 ± 5 mm Hg **	18·3% PASP > 32 mm Hg Hazard ratio for heart failure or death 1·55 (95% CI 1·24 – 1·93) with PASP > 32 mm Hg

HIV: Human immunodeficiency virus; IQR: Interquartile range; LV: Left ventricular; PASP: pulmonary artery systolic pressure; RAP: right atrial pressure; RVSP: right ventricular systolic pressure; SD: standard deviation; TR: tricuspid regurgitant; Yrs: years

*
Assuming a right atrial pressure of 10 mm Hg

**
Assuming a right atrial pressure of 5 mm Hg

†
Derived from TR velocity measurements